

**An epidemiological survey of airways obstruction and bronchial
responsiveness in an adult population**

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ABSTRACT

AIM OF STUDY To assess the relationships between age, respiratory symptoms, airways calibre and nonspecific bronchial responsiveness in a population sample including large numbers of elderly adults.

METHODS Caucasian adults aged ≥ 45 years were selected from lists of GPs in Central Manchester using random number tables, and sent a respiratory symptoms questionnaire (exclusions: housebound, confused). A random sample of those failing to respond after 2 reminders was contacted by 'phone or home visit. Those not excluded from bronchial challenge (exclusions: ischaemic heart disease, oral steroids, beta-blocker or anticholinergic medication) were invited to attend for spirometry, bronchial challenge (using methacholine and Newcastle dosimeter method), and venous blood sampling.

RESULTS 783 questionnaires were sent to eligible subjects; 508 returned the full questionnaire and 215 an abbreviated version (overall response rate 92.3%). 395 subjects were invited to attend; 247 did so, of whom 246 performed spirometry and 208 completed bronchial challenge. Questionnaire responders were representative of study population; attenders were slightly younger. Prevalence of smoking was high (29.2% current smokers, 37.3% ex-smokers). Asthma was reported by 7.3%, bronchitis by 15.4%; a further 7.3% reported both diagnoses. 53.8% of subjects reported one or more respiratory symptoms. Chronic airflow obstruction (defined as $FEV_1/FVC < 60\%$ for age < 65 years; for age ≥ 65 lower limit of FEV_1/FVC was calculated from reference ranges (Enright et al. 1993) was present in 26.4% of the population; bronchial hyper-responsiveness ($PD_{20} < 100\mu g$) was found in 26.0%. Comparison with values calculated from reference ranges suggested that FEV_1 in non-smoking Manchester adults was lower than predicted. Only 55.4% of those with chronic airflow obstruction reported a diagnosis of asthma or bronchitis, and only 35.4% were using appropriate inhaled medications. There was no difference in the prevalence of reported symptoms, diagnoses, or chronic airflow obstruction between adults aged < 65 or ≥ 65 years. Multiple regression analysis with bronchial responsiveness (log dose-response slope) as the dependent variable showed an

independent negative relationship with FEV₁, and positive relationships with age and total IgE level.

CONCLUSIONS Respiratory morbidity is common in this middle-aged and elderly inner-city population, but is frequently undiagnosed and untreated. There is a positive relationship between bronchial responsiveness and age. Atopy is associated with bronchial responsiveness even in older adults.

DEFINITIONS AND ABBREVIATIONS

The terminology of obstructive airways disease is controversial. The considerable difficulty in distinguishing clinically between asthma and smoking-related airways obstruction (particularly in older adults) has led to the use of non-committal terminology (chronic nonspecific lung disease, chronic obstructive bronchitis etc), rather than terms such as asthma and chronic bronchitis, for which standardised definitions are available. ("Chronic obstructive pulmonary disease" is about to be clearly defined, with the publication of new guidelines on its management). In the interests of clarity, the terminology used throughout this thesis is defined below.

ASTHMA: a disease characterised by increased responsiveness of the airways to various stimuli, and manifested by bronchoconstriction which varies spontaneously or secondary to therapy (American College of Chest Physicians - American Thoracic Society Joint Committee on Pulmonary Nomenclature. 1975);

CHRONIC BRONCHITIS: a syndrome of mucus hypersecretion, associated with chronic cough productive of sputum daily for 3 consecutive months in at least 3 consecutive years (Medical Research Council 1960);

CHRONIC AIRFLOW OBSTRUCTION: a persistent obstructive ventilatory impairment detected by spirometry.

The following abbreviations are use throughout this thesis:

PEFR - peak flow rate

FEV₁ - forced expiratory flow in 1 second

FEF₅₀ - forced expiratory flow rate at 50% from vital capacity

FVC - forced vital capacity

GP - general practitioner

Chapter 1: INTRODUCTION AND LITERATURE REVIEW

A) NONSPECIFIC BRONCHIAL RESPONSIVENESS IN ASTHMA AND CHRONIC BRONCHITIS

Nonspecific bronchial responsiveness represents the tendency of the airways to constrict in response to an inhaled stimulus, which may be a physical or chemical agent (for example cold air, histamine, methacholine). The term "nonspecific" refers to the fact that such agents produce bronchoconstriction in all individuals (including those with normal airways) if inhaled in sufficient doses. This differs from bronchial responsiveness to specific allergens, which is dependent on prior exposure and sensitisation.

i) Increased bronchial responsiveness in asthma

It has been known for over 50 years that the inhalation of histamine produces bronchoconstriction in asthmatics (Curry 1946). More recently, studies have shown that increased sensitivity to the broncho-constrictor effect of inhaled histamine or cholinergic agents is almost universal in individuals with current symptomatic asthma (Cockcroft et al. 1977; Townley, RG et al. 1979). Asthmatic subjects show three main differences from normal subjects in their response to inhaled histamine or methacholine. Firstly, they develop bronchoconstriction at a lower dose of inhaled agent than normal subjects (increased sensitivity). Secondly, if dose-response curves are plotted, the slope of the curve is steeper for asthmatic subjects than for normals (increased reactivity) (Orehek et al. 1977). Thirdly, whereas in normal subjects inhalation of increasing doses of histamine/methacholine will eventually fail to produce further bronchoconstriction (producing a "plateau" on the dose-response curve), in many asthmatics there is no evidence of such a plateau, and bronchoconstriction is limited only by the side-effects of the provoking agent (Woolcock et al. 1984). This altered response to inhaled histamine in asthmatic subjects has been variably referred to as both "bronchial hyper-reactivity", "bronchial hyper-responsiveness" and "increased nonspecific bronchial responsiveness"; to avoid confusion, the latter two terms will be used throughout this thesis to represent both increased sensitivity and reactivity to inhaled histamine

or methacholine.

Measurement of bronchial responsiveness has been used in both clinical and epidemiological studies of asthma. Such studies have shown that increased bronchial responsiveness is not specific to asthma, but is also found in a spectrum of other disorders, including atopic rhinitis, chronic bronchitis, cystic fibrosis, and pulmonary oedema. Indeed, in a study of a young population, Cockcroft et al found that 4%-5% of non-atopic, non-asthmatic "normal" individuals also had bronchial hyper-responsiveness (Cockcroft et al. 1985). Consequently, the positive predictive value of increased bronchial responsiveness for a diagnosis of asthma is relatively low: while almost all subjects with current asthma will have increased bronchial responsiveness, only approximately 40% of subjects with increased bronchial responsiveness have definite asthma (Cockcroft et al. 1985; Cockcroft 1988).

Epidemiological surveys show that bronchial responsiveness is continuously distributed throughout the young population, with asthmatic subjects representing a subgroup within the hyper-responsive end of the distribution (Cockcroft and et al. 1983; Cockcroft et al. 1983; Nieminen 1992). However, it has not been possible to identify a cut-off point which convincingly separates asthmatic from non-asthmatic subjects because of the considerable degree of overlap between them. Despite this, a quantitative relationship has been demonstrated between level of bronchial responsiveness and symptom severity, treatment requirements and diurnal peak flow variability in patients with asthma (Juniper et al. 1981; Murray, AB et al. 1981; Brand et al. 1991). Furthermore, changes in bronchial responsiveness were associated with changes in symptom frequency and medication use in a community population survey (Britton et al. 1988a).

ii) Increased bronchial responsiveness in chronic bronchitis

Increased bronchial responsiveness is found in approximately 50% of subjects with chronic bronchitis (Yan et al. 1985; Engel et al. 1989). However, comparisons of bronchial hyper-responsiveness in patients with chronic bronchitis and asthma have

identified important differences between the two diseases. Firstly, the mean level of bronchial responsiveness in patients with chronic bronchitis is usually less than that of patients with current symptomatic asthma, and is approximately equivalent to levels seen in mild asthma or atopic rhinitis (Yan et al. 1985; Engel et al. 1989; Woolcock et al. 1991; Nieminen 1992). Nevertheless, there is considerable overlap, and level of bronchial responsiveness alone does not reliably differentiate between asthma and chronic bronchitis (Yan et al. 1985; Enarson et al. 1987; Cerveri et al. 1988; Engel et al. 1989; Woolcock et al. 1991; Nieminen 1992).

There are also qualitative differences between bronchial hyper-responsiveness in asthma and chronic bronchitis. The slope of the dose-response curve produced when histamine or methacholine is inhaled by a subject with chronic bronchitis is usually intermediate between the steep slope of an asthmatic dose-response curve, and the more gradual incline of a normal curve (Woolcock et al. 1991). There may also be differences in the **shape** of the curve: in chronic bronchitis (as in normals) a plateau is usually reached when maximal bronchoconstriction has occurred - this plateau is not seen in the dose-response curve of subjects with symptomatic asthma (DuToit et al. 1986; Woolcock et al. 1991).

Furthermore, the level of bronchial responsiveness in subjects with both chronic bronchitis and emphysema is strongly associated with the degree of baseline airflow obstruction present (measured as FEV_1 or FEV_1/FVC); this relationship is weaker in subjects with asthma and normal baseline airways calibre (Yan et al. 1985; Mullen et al. 1986; Verma et al. 1988; Woolcock et al. 1991; Ulrik 1993). This observation has led to the suggestion that increased bronchial responsiveness in subjects with chronic airflow obstruction is merely secondary to the decreased airways calibre, rather than the result of a specific disease process (Ramsdale and Hargreave 1990).

Some other differences between bronchial hyper-responsiveness in asthma and chronic bronchitis tend to support this theory. Firstly, the level of bronchial

responsiveness in subjects with chronic bronchitis and chronic airflow obstruction does not show the strong link with measures of disease severity (eg peak flow variability, treatment requirements) that is seen in asthma (James et al. 1988; Brand et al. 1991). Secondly, asthmatic subjects with increased bronchial responsiveness will respond with pronounced bronchoconstriction to a wide variety of inhaled stimuli, including cold air hyperventilation, sulphur dioxide, and propranolol, whereas subjects with chronic bronchitis often fail to respond to these other agents (Ramsdale et al. 1984, 1985b; DuToit et al. 1986; Ramsdale and Hargreave 1990; Woolcock et al. 1991).

However, other characteristics of bronchial hyper-responsiveness in chronic bronchitis suggest that it is **not** merely the result of decreased airways calibre. Increased bronchial responsiveness may be present in smokers with **normal** baseline FEV₁, but is not invariable in smokers with chronic airflow obstruction (Taylor et al. 1985b; Yan et al. 1985). Moreover, pre-treatment with bronchodilators may reduce bronchial responsiveness in subjects with chronic airflow obstruction, without significantly increasing baseline FEV₁ (Yan et al. 1985); pre-treatment with salbutamol and ipratropium had different effects on bronchial responsiveness despite producing the same degree of bronchodilatation (Britton et al. 1988c). In one study of the effect of prior bronchoconstriction on bronchial responsiveness in normal subjects, histamine challenge was performed following inhalation of either nebulised saline or methacholine (Chung and Snashall 1984). Although inhalation of methacholine increased airways resistance before the start of the histamine challenge, the level of bronchial responsiveness was not affected, suggesting that the result of the histamine challenge was not merely a direct reflection of the pre-challenge airways calibre.

Longitudinal studies monitoring airways calibre and bronchial responsiveness over time have failed to clarify this area. A 4 year study of 27 smokers and 16 ex-smokers found that smokers with increased bronchial responsiveness had an accelerated decline in FEV₁ (Taylor et al. 1985b). However, this decline in FEV₁

was accompanied by a further increase in bronchial responsiveness, raising the possibility that the bronchial hyper-responsiveness was the result of, rather than the cause of, the low FEV₁ (Lim et al. 1988). In contrast, Postma et al studied 81 non-allergic current or ex-smokers with chronic airflow obstruction for 2-21 years, and found that the faster rate of FEV₁ decline in those with bronchial hyper-responsiveness was independent of baseline airways calibre (Postma et al. 1986).

Longitudinal studies of subjects **without** chronic bronchitis likewise give conflicting results. A survey of 2280 healthy men (excluding those with asthma, chronic bronchitis or respiratory symptoms) found an initial correlation between airways calibre and bronchial responsiveness, but subsequent changes in bronchial responsiveness were not related to either baseline or annual change in FEV₁ (Sparrow et al. 1994). However, in 35 asthmatics studied over 6 months, 35% of between-subject variation and 45% of within-subject variation in bronchial responsiveness could be attributed to differences in pre-challenge FEV₁ (Dirksen et al. 1992).

Studies suggesting that increased bronchial responsiveness predisposes to accelerated rate of decline in airways calibre have been taken as supporting evidence for the "Dutch hypothesis". This was developed in the 1960s after a cross-sectional population survey in Holland found that FEV₁ had a stronger relationship with measures of atopy than with smoking. The hypothesis proposed that underlying "host factors" determined which smokers would develop chronic airflow obstruction, and atopy and bronchial hyper-responsiveness were suggested as the host factors involved (Orie et al. 1961; van der Lende et al. 1969). Despite some supportive evidence for the Dutch hypothesis, other longitudinal population surveys have produced contradictory results (Burrows et al. 1987).

In summary, it is clear that although bronchial responsiveness is increased in a proportion of subjects with chronic bronchitis, there are both similarities and differences between the bronchial hyper-responsiveness seen in chronic bronchitis

and asthma. This suggests that the mechanisms producing the increase in bronchial responsiveness may differ between the two disease processes. As yet it is still unclear whether bronchial hyper-responsiveness in chronic bronchitis is the cause of, or the consequence of, decreasing airways calibre (Dosman et al. 1990).

B) METHODS OF MEASUREMENT OF NONSPECIFIC BRONCHIAL RESPONSIVENESS

Nonspecific bronchial responsiveness is measured by monitoring airways calibre whilst giving measured doses of inhaled stimulus under controlled conditions. Unfortunately, several versions of this "bronchial challenge" technique are available, differing in the challenge agent inhaled, the method of administration of this agent, the method of measurement of airways calibre, and in the parameter used to express the challenge result. In an attempt to standardise these various methods, the European Respiratory Society has published an official statement of recommendations for measurements of bronchial responsiveness (Sterk et al. 1993). Some of the techniques currently in use will be briefly discussed below.

i) Choice of challenge agent

Pharmacological agents such as histamine or methacholine are more often used than physical agents for the measurement of bronchial responsiveness. Both histamine and methacholine stimulate contraction of bronchial smooth muscle, but do so by different mechanisms. Histamine acts on H1 receptors, and may also stimulate cholinergic pathways producing vagally mediated effects; methacholine stimulates muscarinic postganglionic parasympathetic receptors producing bronchial wall smooth muscle contraction (Pratter and Irwin 1984). Despite these different actions, the results of bronchial challenge with the two agents are similar (Juniper et al. 1978, 1981; Hargreave et al. 1981). However, they are not interchangeable: in one comparison using identical protocols in stable asthmatic subjects, bronchial responsiveness measured with histamine was 3.5 times higher than with methacholine (Connolly et al. 1988a). Whilst methacholine is accepted to have a cumulative bronchoconstrictive effect when administered in sequential increasing doses, there is disagreement whether histamine has a cumulative or non-cumulative action (Juniper et al. 1978; Connolly et al. 1988a). As methacholine has fewer adverse effects, it is the agent of choice for large studies of bronchial responsiveness.

ii) Method of administration of challenge agent.

Both histamine and methacholine are prepared as solutions, and so must be nebulised for inhaled administration. Recommendations for the preparation and storage of solutions of histamine and methacholine for bronchial challenge have been made by the European Respiratory Society (Sterk et al. 1993).

To allow administration of accurate doses of nebulised agent, nebuliser output must be standardised. Various different types of nebuliser are commercially available, having different outputs and producing particles of differing sizes. In a comparative study using three different nebuliser types in identical bronchial challenge protocols, nebulisers of different models and different nebulisers of the same model produced different outputs and particle sizes (Ryan et al. 1981a). Nebuliser output varied with flow rate, and bronchial challenge result was significantly altered by changes in nebuliser output but not by particle size.

Accurate calibration of nebuliser output is thus essential to ensure precision in the dose of challenge agent being administered. Traditionally, output has been assessed by nebuliser weight loss during a period of nebulisation. However, this assumes that all solution lost from the nebuliser is the result of nebulisation, whereas in fact there is also significant loss of solvent by evaporation (Cockcroft et al. 1989). Consequently, nebuliser calibration by weight loss will over-estimate aerosol output.

Direct measurement of nebuliser output using a solute tracer and aerosol impaction can also be performed (Dennis et al. 1990). Using this method, it has been confirmed that continuous nebulisation causes cooling of the reservoir solution in the nebuliser, and increases the concentration of solute due to evaporation of solvent. Weight loss during nebulisation, but not output of solute, increases substantially with the temperature of the reservoir solution, as a result of increased evaporation. However, both weight loss and solute output are dependent on flow rate. Thus flow rate should be standardised for all bronchial challenges, which should be carried out at a constant ambient temperature. Nebuliser reservoir solutions should be replaced

regularly to minimise the effects of decreasing temperature and increasing concentration (Sterk et al. 1993).

Once the nebuliser has been adequately calibrated, there are three different methods of administering the nebulised challenge agent to the subject: the tidal breathing method, the dosimeter method, and the Yan method. In the **tidal breathing method**, the nebuliser is calibrated to give a known output of challenge agent per minute, and the subject inhales sequential doubling concentrations of nebulised challenge agent by normal tidal breathing. Each concentration of challenge agent is inhaled for 2 minutes, with 5 minutes break between successive concentrations (Cockcroft et al. 1977; Hargreave et al. 1981). Spirometry is performed before the test and following each 2 minute inhalation period; the test ends when lung function has fallen by 20%.

The **dosimeter method** for bronchial challenge allows estimation of the **dose**, rather than the concentration, of challenge agent producing a particular change in lung function. The dosimeter itself is an electronic timing device which operates the nebuliser for the precise periods of time necessary to administer a particular dose of challenge agent (Hendrick et al. 1986). The nebuliser is only operated during inspiration, with the start of nebulisation being triggered either by a flow sensor, or by the test operator. Nebulisers are calibrated so that output per second is known, and then the time period of nebulisation required to produce a 10 μ l output of solution per actuation is calculated for each nebuliser and programmed into the dosimeter. Sequential doubling doses of nebulised challenge agent are given at 5 minute intervals; each dose is inhaled during 5 inspiratory capacity breaths, each lasting 5 seconds, with no delay between breaths. Spirometry is performed at the start of the test, and then immediately before administration of the next dose. As with the tidal breathing method, the test ends when spirometry results fall by 20%.

The Yan method has been widely used in epidemiological studies as it uses a portable hand-held nebuliser and does not need a fixed air supply (Yan et al. 1983). The nebuliser is operated by squeezing, and is triggered at the start of two 3-second

inhalations, each of which is followed by breath-holding for 3 seconds. The different doses of challenge agent are given by varying both the number of breaths taken and the concentration of the solution of challenge agent.

The dosimeter method has several theoretical advantages over the tidal breathing and Yan methods. Firstly, the activation of the nebuliser only during inspiration prevents wastage of nebulised challenge agent during expiration. Secondly, the use of controlled 5-second inhalations, standardised for all subjects, reduces variation in particle deposition throughout the lung caused by variation in breathing patterns (Ryan et al. 1981a; Bennett and Smaldone 1987). Thirdly, accurate control of nebuliser timing should allow more precise determination of the dose of challenge agent administered.

In fact, comparisons between tidal breathing, dosimeter, and Yan methods have in general shown similar results with all 3 methods. Ryan et al found that a tidal breathing method and a dosimeter method gave similar measurements of bronchial responsiveness, and were equally reproducible (Ryan et al. 1981b). Britton et al compared the tidal breathing and Yan methods with a method using an ultrasonic nebuliser; reproducibility was similar for all 3 methods, but tidal breathing gave readings 1.75-2.3 doubling concentrations lower than the other two methods (Britton et al. 1986). Knox et al compared Yan and dosimeter methods, and found that the Yan method gave slightly lower measurements of bronchial responsiveness than the dosimeter; reproducibility was similar for both techniques, and improved with the experience of the subject (Knox et al. 1991). Beach et al compared dosimeter and tidal breathing methods and found better reproducibility of recordings with the dosimeter (Beach et al. 1993). However, examination of the results showed that the different reproducibilities of the two methods were the result of the different methods of measuring lung function, rather than the differing methods of delivery of the challenge agent.

iii) Measurement of airways calibre during bronchial challenge

The parameter most frequently used as a measure of airways calibre during bronchial challenge is FEV₁. Measurement of FEV₁ is simple to perform, does not require complex or expensive equipment, and is reproducible. Peak flow is also simple to perform, but tends to be less reproducible than FEV₁ (Connolly et al. 1988b). Other measures are more sensitive to small changes in airways calibre than FEV₁, but require the use of complex equipment (eg airways resistance), or are less reproducible (eg FEF₅₀, FEF₃₅) (Dehaut et al. 1983).

The timing and number of spirometric measurements during bronchial challenge also varies between different challenge protocols. Dosimeter techniques commonly use the mean of a fixed number (3-6) of repeated FEV₁ manoeuvres performed immediately before each subsequent dose of challenge agent (Hendrick et al. 1986). In contrast, the tidal volume technique described by Cockcroft et al uses the lower of two FEV₁ measurements performed 0.5 and 1 minute following each inhalation (Cockcroft et al. 1977).

Using the mean of several recordings will reduce the effect of variable technique and so improve accuracy (Ullah et al. 1983). This was demonstrated by a comparison between dosimeter and tidal breathing methods, which found that the superior reproducibility of the dosimeter technique resulted from the use of the mean of 6 readings of FEV₁ rather than the lowest of two (Beach et al. 1993). However, the use of multiple FEV₁ manoeuvres may itself cause bronchodilatation (as the result of repeated maximal inspiration), which could in theory alter results (Orehek et al. 1981). Furthermore, there is a risk of producing fatigue, which can adversely affect performance (Tager et al. 1976). In theory, this might be a particular problem in elderly subjects; in practise, a dosimeter technique using the mean of three measurements of FEV₁ prior to each inhaled dose of challenge agent was well tolerated and reproducible in subjects over 65 years (Connolly et al. 1988b).

iv) Expression of results

The results of bronchial challenge are usually expressed as either the dose (dosimeter technique) or concentration (tidal breathing technique) of challenge agent producing a 20% fall in baseline lung function. This parameter is termed the provoking dose or concentration of challenge agent (PD_{20} or PC_{20}). However, if the decrease in lung function during bronchial challenge is $<20\%$, these parameters cannot be calculated, thus data is censored at lower levels of bronchial responsiveness. This is a particular problem in cross-sectional population surveys, where the majority of subjects tested are not asthmatic, and has led to a search for other parameters which can be calculated even if there is little change in lung function during bronchial challenge.

Alternative parameters proposed have included the area under the dose-response curve, and methods involving extrapolation of the curve beyond the final dose of challenge agent given. These methods increase the number of subjects for whom the bronchial challenge result can be quantified, but require relatively complex calculations (Chinn et al. 1987; Hopp et al. 1987). A more simple method is to summarise each dose-response curve by calculating the slope of a line extending from the origin to the last data point obtained (the "dose-response slope", DRS) (O'Connor et al. 1987). In one population survey of bronchial responsiveness, PD_{20} could only be calculated for 8% of the sample, and extrapolation of PD_{20} using a curve-fitting method produced a result in only half of the remaining cases; in contrast, the dose-response slope could be calculated for all subjects, and was highly reproducible (Abramson et al. 1990).

Some authors have expressed reservations about the sensitivity and reproducibility of the dose-response slope, particularly in subjects with low levels of bronchial responsiveness (Cockcroft and Berscheid 1983; Bruschi et al. 1989; Higgins et al. 1989a; Seppala 1991; Trigg and Davies 1991). However, several published epidemiological surveys have now used both dose-response slope and PD_{20} as measures of bronchial responsiveness: the fact that dose-response slope can be easily

calculated for all subjects studied make it the parameter of choice for cross-sectional surveys of bronchial responsiveness (Peat et al. 1991, 1992b; Rijken et al. 1993a; Sparrow et al. 1994; Trigg et al. 1994).

C) PATHOPHYSIOLOGY OF INCREASED NONSPECIFIC BRONCHIAL RESPONSIVENESS

Whilst many factors have been shown to influence bronchial responsiveness, the relative contributions of these in asthma and chronic bronchitis is unclear. It is also possible that different mechanisms are involved in these different disease processes. There is evidence that both genetic and environmental factors are involved in the pathogenesis of asthma (Burney 1992; Paoletti et al. 1992). The genetic component may be linked to an inherited atopic tendency (Peat et al. 1992c), or to polymorphism of the beta-adrenoceptor (Hall et al. 1995). The environmental triggers involved have not been fully identified, but may include viral infections (Empey et al. 1976), respiratory infections in infancy, and/or environmental pollutants (Burney 1992; Paoletti et al. 1992). The most important environmental trigger for chronic bronchitis is cigarette smoke exposure, but the factors determining whether or not an individual smoker will develop chronic airflow obstruction are not clear.

Three mechanisms identified as possible causes of bronchial hyper-responsiveness in asthma and chronic bronchitis are abnormalities of bronchial smooth muscle, inflammation of the bronchial wall epithelium, and altered autonomic control of airway calibre. These are discussed below.

i) Abnormality of bronchial smooth muscle

Biopsy and post-mortem specimens of lung tissue from patients with asthma or chronic bronchitis show evidence of smooth muscle hypertrophy (Hogg 1990). This could in theory increase bronchial responsiveness by exaggerating the effect of a contractile stimulus (Moreno et al. 1986; James et al. 1989), and by reducing the elastic recoil of the airways. However, it is difficult to envisage this as the cause of the rapid fluctuations in airways calibre seen in asthma.

Alternatively, the sensitivity of bronchial smooth muscle to contractile stimuli could

be increased in asthma (Black 1991). However, several studies have failed to show a correlation between in vivo bronchial responsiveness to histamine or methacholine and in vitro sensitivity of isolated airway preparations to the same agonists (Holgate et al. 1987; Hogg 1990; Black 1991). This does not support the existence of an intrinsic smooth muscle abnormality in asthma.

There is some evidence that the sensitivity of bronchial smooth muscle to contractile stimuli may be influenced by inflammatory mediators (eg mast cell-derived prostaglandins and thromboxane) (Jongejan et al. 1990). Thus it is possible that abnormal smooth muscle contraction in asthma could result not from a primary muscle abnormality, but from the effects of bronchial wall inflammation.

ii) Inflammation of bronchial wall

It is now widely accepted that inflammation is involved in the pathophysiology of both chronic bronchitis and asthma, although the inflammatory cells and mediators involved may differ between the two disease processes (Jeffery 1991; Barnes and Lee 1992). Endobronchial biopsies from asthmatic subjects have shown an infiltrate of chronic inflammatory cells, and pathological specimens from subjects dying of acute asthma show evidence of acute inflammation (Chung 1986; Beasley et al. 1989; Hogg 1990). The level of immune activity of infiltrating inflammatory cells is reflected in the level of HLA-DR expression: this has been shown to correlate with the level of bronchial responsiveness to histamine (Poulter et al. 1990).

Several of the stimuli increasing bronchial responsiveness in asthma (eg inhaled allergens and viral infections) cause inflammation of the bronchial epithelium (Djukanovic et al. 1990). The increased bronchial responsiveness caused by inhaled ozone has been shown to correlate with the intensity of inflammatory response (Holgate et al. 1987). Bronchial wall inflammation results in the release of mast cell mediators (Chung 1986; Townley, RJ and Hopp 1987); measured levels of some of these correlate with bronchial responsiveness in asthmatic patients (Djukanovic et al. 1990).

Mast cell-derived mediators are capable of producing many of the abnormalities seen in pathological specimens from patients with asthma (Chung 1986; Holgate et al. 1987; Townley, RJ and Hopp 1987). Lymphokines released from inflammatory cells may also alter beta-adrenoceptor function, and so may be responsible for some of the abnormalities in the beta-adrenergic system seen in subjects with asthma (see below) (Nijkamp and Henricks 1990). Thus, the increased bronchial responsiveness seen in asthma could be explained by interactions between inflammatory cells, mediators and bronchial smooth muscle and its neural control (Chung 1986).

Bronchial wall inflammation could also contribute to bronchial responsiveness by increasing the thickness of the bronchial wall. A study of postmortem lung specimens taken from patients with asthma confirmed increased thickness of membranous and cartilaginous airway mucosa and submucosa (James et al. 1989). As a result, less smooth muscle shortening was required to occlude the lumen, although baseline airways resistance was only slightly increased. However, the authors commented that the geometric consequences of altered airways structure could not entirely explain the marked airways hyper-responsiveness seen in asthma.

Chronic bronchitis is characterised by mucus hypersecretion and enlargement of submucosal glands; this may also be associated with inflammation of bronchiolar walls (Jeffery 1991). In smokers undergoing surgery for bronchogenic carcinoma, pre-operative bronchial responsiveness was related to the degree of bronchiolar inflammation in the resected lung (Mullen et al. 1986). Differences have been found between the inflammatory infiltrates in the airways of asthmatic and chronic bronchitic subjects (Laitinen and Laitinen 1991).

iii) Altered autonomic control

Autonomic nerves have effects on airway smooth muscle, bronchial vessels and mucous glands, and thus could contribute to airway narrowing in both asthma and chronic bronchitis (Barnes 1987; De Jongste et al. 1991). Both sympathetic and parasympathetic nervous systems innervate the lung, and there is also evidence that

a third "non-adrenergic non-cholinergic" (NANC) system may be involved (Barnes 1984). An imbalance between the effects of the cholinergic and sympathetic nervous systems was suggested as a cause of asthma as long ago as 1921 (Alexander and Paddock 1921); the possible contributions of the different nervous systems to increased bronchial responsiveness in asthma and chronic bronchitis will be discussed below.

a) Parasympathetic (cholinergic) nervous system

There is direct innervation of the walls of the major bronchi by cholinergic nerves originating in the vagus and synapsing in ganglia within the bronchial wall. Inhaled cholinergic antagonists (eg ipratropium) cause bronchodilatation in normal individuals, indicating a degree of resting cholinergic bronchoconstrictor tone. Activation of these cholinergic nerves (by reflex mechanisms or stimulation of afferent bronchial wall irritant receptors) produces bronchoconstriction; this is thought to be one of the mechanisms by which histamine alters bronchial calibre.

Although cholinergic agonists produce exaggerated pupillary responses in asthmatic and atopic subjects compared with normals, there is no direct evidence that cholinergic tone is increased in asthma (Barnes 1986). The fact that anticholinergic agents produce relatively more bronchodilatation in chronic bronchitis than in asthma implies a more important role for increased cholinergic tone in the pathophysiology of chronic bronchitis (van Schayck et al. 1991). Possible mechanisms of such enhanced cholinergic activity could include potentiation by inflammatory mediators, defects in pre- or post-junctional receptor function, or increased end-organ responsiveness to acetylcholine (Barnes 1986; De Jongste et al. 1991). Alternatively, airways inflammation could increase reflex vagal activity by exposing sensory nerve endings to nonspecific irritants.

b) Sympathetic (adrenergic) nervous system

Although there is no direct sympathetic innervation of the bronchi, both alpha and beta-adrenoceptors are found in the lungs. These receptors may bind circulating

endogenous catecholamines: control of beta-adrenoceptor density and binding affinity by circulating catecholamine levels has been demonstrated in normal volunteers (Fraser, J et al. 1981; Feldman et al. 1983). There is evidence of defective catecholamine release in some asthmatics: post-exercise catecholamine levels are lower in subjects with exercise-induced asthma, and catecholamine levels do not increase even in acute severe asthma (Barnes 1987).

The majority of evidence suggests that beta rather than alpha-adrenoceptors are involved in the pathogenesis of asthma. Alpha-adrenoceptors are sparse in the lung, although may be increased in chronic bronchitis. Some studies have shown increased alpha-receptor responsiveness in asthma, and receptor stimulation can under some conditions cause contraction of airways smooth muscle and submucosal gland secretion (Barnes 1986). However, alpha-receptor blockers do not alter lung function or bronchial responsiveness in asthmatics (Barnes 1986, 1987).

Beta-adrenoceptors are widespread throughout small and large airways smooth muscle, epithelial cells, and submucosal mucus glands (Carstairs et al. 1985). Beta-adrenoceptor agonists not only promote bronchial smooth muscle relaxation, but also may increase mucociliary clearance (Pavia et al. 1980; Phipps et al. 1982), stabilise mast cells (Peters et al. 1982) and reduce vascular permeability (Persson et al. 1982). Thus defective beta-adrenoceptor function might be expected to produce several of the airways abnormalities seen in asthma.

The observation by Szentivanyi and colleagues that intraperitoneal administration of Bordetella pertussis in animals induced both increased airways sensitivity to histamine and decreased response to beta-adrenoceptor agonists revived the theory of beta-adrenoceptor dysfunction as a cause of asthma (Szentivanyi 1968). Since then, numerous in vitro and in vivo studies of beta-adrenoceptor density and activity have been performed, some of which support this hypothesis. However, there is no convincing evidence to suggest that altered beta-adrenoceptor activity is present in patients with chronic bronchitis (De Jongste et al. 1991).

The fact that beta adrenergic antagonists cause bronchoconstriction in asthmatic but not normal subjects suggests that resting airways tone is maintained by sympathetic drive in asthma (McNeill 1964). Furthermore, asthmatic subjects have diminished pulse rate and metabolic responses to beta-agonists (Lockey et al. 1967; Grieco et al. 1968; Middleton and Finke 1968; Bernstein et al. 1972). Moreover, monitoring of blood pressure, pupillary responses and cutaneous blood flow showed evidence of beta-adrenoceptor hyporeactivity and increased cholinergic and alpha-adrenergic responses in patients with asthma and allergic rhinitis compared with controls (Kaliner et al. 1982; Lemanske and Kaliner 1990).

Direct measurement of alpha- and beta-adrenoceptor number and function has been possible following the identification of such receptors on human peripheral leukocytes, and the demonstration of similarities between these and lung adrenoceptors (Conolly and Greenacre 1977; Goldie et al. 1984). Using this model, several authors have shown abnormalities of both receptor number (Brooks et al. 1979; Kariman 1980), and function (Parker and Smith 1973; Connolly et al. 1992b; Nielson et al. 1992) in patients with asthma.

A major confounding factor in such research is the use of beta-agonist medications by the majority of patients with asthma. The discovery of tachyphylaxis in response to beta-agonist stimulation raised the possibility that the *in vivo* and *in vitro* beta-adrenoceptor abnormalities demonstrated in asthmatics may be the result of beta-agonist therapy (Morris 1980). *In vitro*, prolonged exposure to beta-agonists leads to desensitization of mononuclear cell beta-adrenoceptors (Galant et al. 1978; Conolly et al. 1979). Despite this, there is little evidence for a clinically significant reduction in bronchodilator response following prolonged beta-agonist therapy *in vivo* (Harvey and Tattersfield 1982; Schuster et al. 1991). It is possible that blood mononuclear cell beta-adrenoceptors are more susceptible to agonist-induced down-regulation than lung beta-adrenoceptors (Svedmyr et al. 1976; Tashkin et al. 1982).

The influence of beta-agonists can be overcome by studying patients who have never

used this treatment. Beta-adrenergic hyporesponsiveness has been demonstrated in vivo in untreated subjects with allergic rhinitis (Kaliner et al. 1982; Lemanske and Kaliner 1990). More significantly, a study of mild asthmatics never treated with beta-agonists found inverse relationships between bronchial responsiveness in vivo, and in vitro measurements of mononuclear cell beta-adrenoceptor density, binding affinity and functional response to beta agonist (Connolly et al. 1992b; Nielson et al. 1992). However, the importance of intrinsic beta-adrenoceptor abnormalities in the pathogenesis of asthma and other forms of airflow obstruction remains unclear.

Beta-adrenoceptor autoantibodies have been described in a small proportion of patients with asthma or allergic rhinitis, as well as some normal individuals (Venter and Fraser 1980; Fraser and Venter 1982). Moreover, decreased beta-adrenergic sensitivity was demonstrated in autoantibody-positive individuals (Venter and Fraser 1985). In a population of 376 asthmatic children, beta-receptor autoantibodies were found in 8.8% of severe asthmatics and 3.4% of mild asthmatics (Blecher 1984; Fraser, CM and Venter 1984). Thus it is possible that in a small subset of patients with asthma, the presence of auto-antibodies to beta-adrenoceptors mediates autonomic dysfunction and contributes to the pathogenesis of the disease.

Some of the abnormalities of beta-adrenergic function described in asthma are similar to changes occurring as part of the normal ageing process. In vivo, the heart rate response to isoprenaline decreases progressively with age (Vestal et al. 1979; Bertel et al. 1980; Fitzgerald et al. 1984), and plasma noradrenaline levels are higher in older than younger subjects (Krall et al. 1981). In vitro, lymphocytes of healthy elderly subjects have been shown to have similar beta-adrenoceptor density, but reduced receptor response to agonists when compared with those of younger subjects (Dillon et al. 1908; Abrass and Scarpace 1981, 1982; Doyle et al. 1981; Krall et al. 1981; Heinsimer and Lefkowitz 1985). A study of non-asthmatic and asthmatic young and elderly subjects confirmed normal mononuclear leucocyte beta-adrenoceptor density, but reduced receptor binding affinity in elderly normal subjects; binding affinity was further reduced in elderly asthmatics (Connolly et al.

1994). In contrast, young asthmatic subjects had normal beta-adrenoceptor binding affinity, but reduced density when compared with young normals. Bronchial responsiveness was related to receptor affinity in all subject groups, but a relationship between receptor density and bronchial responsiveness was seen only in young asthmatic subjects.

If decreased beta-adrenergic function contributes to increased bronchial responsiveness in asthma, then it might also be expected that the decrease in beta-adrenergic function occurring as a part of normal ageing would lead to an increase in bronchial responsiveness with age. Epidemiological evidence for and against a change in the prevalence of bronchial hyper-responsiveness with age is discussed below (page 55).

c) Non-adrenergic non-cholinergic system

There has been evidence for some time for the existence of a further inhibitory neural pathway which does not respond to either adrenergic or cholinergic stimuli (Boushey et al. 1980; Barnes 1984). Despite much research, the nature of the neurotransmitter involved in these non-adrenergic non-cholinergic (NANC) inhibitory nerves is unclear, although it is believed to be a neuropeptide (Barnes 1984).

Defective function of this system could in theory contribute to increased bronchial responsiveness. However, there is as yet no firm evidence that this is the case: further research into the nature of the neurotransmitters involved in the NANC system, and into ways of influencing NANC activity is awaited.

D) EPIDEMIOLOGY OF ASTHMA, CHRONIC BRONCHITIS, CHRONIC AIRFLOW OBSTRUCTION, AND NONSPECIFIC BRONCHIAL RESPONSIVENESS

i) Methods of estimating the prevalence of asthma, chronic bronchitis and chronic airflow obstruction

Several epidemiological surveys have described the prevalence and associations of asthma and chronic bronchitis in different populations; some of these are summarised in tables 1.1-1.3. These results have been obtained over a time period of at least 20 years; changes in smoking habits and environmental conditions over the same time period complicate direct comparison between studies.

Unfortunately, there is no universally agreed definition of asthma, and no consensus on which symptoms or investigations are essential to establish this diagnosis (Gross 1980). Consequently, different surveys have used different defining criteria, and the results are not directly comparable. Furthermore, the relationship between asthma and other parameters may be influenced by the definition of asthma. For example, a study defining atopy as an essential feature of asthma is likely to find strong relationships between asthma and measures of atopy (eg skin test results, total IgE levels) (Tager et al. 1987).

Methods used to identify asthma in epidemiological surveys include **questionnaires** to identify subjects reporting physician-diagnosed asthma or asthma-associated symptoms; **clinical examination** of subjects by a physician; **spirometric measurements**, with or without measurement of response to inhaled bronchodilators ("reversibility"); and measurement of bronchial responsiveness by **bronchial challenge**. None of these methods can be regarded as a gold-standard test for the detection of asthma (Samet 1987; Woolcock 1987). Similarly, studies of the prevalence of chronic bronchitis have used questionnaires about respiratory symptoms and smoking habits, and pulmonary function tests have been used to 1-assess the population prevalence of chronic airflow obstruction.

Table 1.1: EPIDEMIOLOGICAL SURVEYS OF RESPIRATORY SYMPTOMS AND LUNG FUNCTION

PRINCIPAL AUTHOR	POPULATION: SAMPLE TYPE	NUMBER	AGE RANGE	RESPONSE RATE	METHODS	CURRENT SMOKERS	EX-SMOKERS
Bakke 1991	Hordaland, Norway Random	4493	18-73	90%	Q A M	40%	26%
Boezen 1995	Groningen, Holland Age-stratified random	836	20-70	56%	Q S		
Britton 1994	Nottingham, UK Systematic	2644	18-70	48%	Q A M	23%	28%
Broder 1974	Tecumseh, USA Whole population	9226	<4 - >75	82%	Q E		
Burney 1987	Hampshire, UK Whole population	873	18-64	61%	Q H		
Burr 1979	South Wales, UK Systematic	418	70-101	86%	Q S	43% ^m 18% ^f	43% ^m , 10% ^f
Caird 1972	Glasgow, UK Age-stratified random	300	65+	70%	Q S	73% ^m 23% ^f	
Cerveri 1988	Lombardy, Italy Age-stratified random	654	15-65	71%	Q E M	30%	
Dow 1991	Southampton, UK Age-stratified random	2161	65-96	84%	Q M	17%	42%
Higgins 1988	Nottingham, UK Systematic	145	18-75	73%	Q A H M		
Higgins 1993	Kesteven, UK Systematic	495	18-65	64%	Q M	37%	19%

Q=questionnaire; A=assessment of atopy; E=physician examination; S=spirometry;
H=histamine challenge; M=metacholine challenge; m=male; f=female

Table 1.2: EPIDEMIOLOGICAL SURVEYS OF RESPIRATORY SYMPTOMS AND LUNG FUNCTION

PRINCIPAL AUTHOR	POPULATION: SAMPLE TYPE	NUMBER	AGE RANGE	RESPONSE RATE	METHODS	CURRENT SMOKERS	EX- SMOKERS
Horsley 1993	New Forest, UK Age-stratified random	1803	65+	96%	Q M	14%	43%
Isoaho 1994	Lieto, Finland Whole population	1396	64-97	93%	Q S	15% <i>m</i> 3% <i>f</i>	55% <i>m</i> 6% <i>f</i>
Krzyzanowski 1990	Cracow, Poland Random	3047	18-70		Q S	63% <i>m</i> 22% <i>f</i>	14% <i>m</i> 4% <i>f</i>
Lebowitz 1975	Tucson, Arizona MSC	3805	<15 - >65	55%	Q A S	43% <i>m</i> 35% <i>f</i>	30% <i>m</i> 18% <i>f</i>
Lundback 1991	Norbotten, Sweden Whole population	5698	35-6, 50-1, 65-6	86%	Q S M	34% <i>m</i> 30% <i>f</i>	
Menezes 1994	Pelotas, Brazil Random	1053	40+	90%	Q	34%	
Milne 1972	Edinburgh, UK Random	487	62-90	65%	Q S	62% <i>m</i> 18% <i>f</i>	
Mortagy 1986	Southampton, UK Systematic	3189	mean 48	71%	Q H		
Neukirch 1995	French cities Random	7203	20-44	75%	Q		
Parameswaran 1995	Sunderland, UK Whole population	1362	65+	70%	Q E		
Samet 1982	Bernalillo, Mexico Age-stratified random	1671	<35 - >64	72%	Q	28% <i>m</i> 25% <i>f</i>	

Q =questionnaire; A=assessment of atopy; H=histamine challenge; M=methacholine challenge
S=spirometry; E=physician examination; MSC=multistage stratified cluster; m= male; f=female

Table 1.3: EPIDEMIOLOGICAL SURVEYS OF RESPIRATORY SYMPTOMS AND LUNG FUNCTION

PRINCIPAL AUTHOR	POPULATION; SAMPLE TYPE	NUMBER	AGE RANGE	RESPONSE RATE	METHODS	CURRENT SMOKERS	EX- SMOKERS
Schachter 1984	Lebanon, USA Whole population	1303	7+		Q S	24% ^m 21% ^f	21% ^m 11% ^f
Trigg 1990	Surrey, UK Systematic	366	18-75	35%	Q A M	29%	27%
van der Lende 1973	Vlaagtwedde/Vlaardingen Random	4692	15-64		Q A H	67% ^m 39% ^f	
Viegi 1991	Po River Delta, Italy (1) MSC	3289	8-64	78%	Q	40%	9%
Viegi 1991	Po River Delta, Italy (2) MSC	2841	8-73	56%	Q M	44% ^m 31% ^f	35% ^m 21% ^f
Viegi 1991	Pisa, Italy MSC	3866	5-90	77%	Q	48% ^m 35% ^f	34% ^m 14% ^f
Woolcock 1987	Busselton, Australia Random	3941	18-88	66%	Q A H	20%	24%
Peat 1992	Busselton, Australia Random	5020	18-55	56%	Q A H	15%	29%

Q =questionnaire; A=assessment of atopy; H=histamine challenge; M=metacholine challenge
S=spirometry; MSC=multistage stratified cluster; m=male; f=female

ii) Estimated prevalence of self-reported asthma and chronic bronchitis

Perhaps the simplest method of measuring the prevalence of a disease is to ask subjects whether they have ever received this diagnosis. The accuracy of this method depends not only on the subject's memory, but also on the diagnostic methods and communication skills of their doctor. Despite this, several population surveys of asthma have relied solely on this method of disease detection; it has been used less commonly in studies of chronic bronchitis.

One obvious problem with the use of self-reported diagnoses of asthma or chronic bronchitis is the similarity in symptoms associated with these two disorders, and the lack of established diagnostic criteria with which to distinguish between them. This can lead to patients receiving multiple diagnostic labels for the same respiratory symptoms. For example, in the Tucson survey (table 1.2) approximately half of subjects aged ≥ 65 years reporting asthma also reported chronic bronchitis and/or emphysema (Dodge and Burrows 1980). Furthermore, when the symptoms and pulmonary function of individuals reporting either asthma or chronic bronchitis (or emphysema) have been compared, there has been considerable overlap between the different diagnoses (Dodge et al. 1986). In one study, the particular diagnostic label given seemed to be influenced more by social class and gender than by symptoms or lung function (Littlejohns et al. 1989).

The accuracy of self-reported diagnoses has also been questioned by studies comparing self-reported asthma and chronic bronchitis with diagnoses recorded in medical records. A study of 14404 Americans found substantial under-reporting of diagnoses, particularly by older individuals, with under-reporting being greater for the diagnosis of chronic bronchitis than for asthma (McWhorter et al. 1989). The opposite was found in a British study, where 8.7% of the study population reported that they had at some time suffered from asthma, but only 4.9% had a diagnosis of asthma recorded by their general practitioner (Trigg et al. 1990). In a preliminary report of a study of adults aged ≥ 65 years, although 24.4% of subjects were thought to have asthma on the basis of symptoms and spirometry, only 7% of these

were aware that they might have asthma (Parameswaran et al. 1995).

Furthermore, studies including both the question "have you ever had asthma/chronic bronchitis", as well as "have you ever been diagnosed as having asthma/chronic bronchitis by a doctor", have identified a small proportion of subjects who answered affirmatively to the first question but not the second (Lundback et al. 1991; Viegi et al. 1994a). The significance of "self-diagnosed" asthma (ie not diagnosed by a doctor) is unclear. In the Tucson study, subjects with an unconfirmed diagnosis of asthma tended to be diagnosed as asthmatic by their physician during subsequent years (Dodge et al. 1986). However, in Tecumseh only 53% of subjects reporting "self-diagnosed" asthma were judged to have asthma by the study physician (Broder et al. 1974). Thus relying on self-reported diagnoses of asthma or chronic bronchitis may not be a reliable method of detecting these conditions in an adult population.

Table 1.4 summarises the results of studies measuring the prevalence of self-reported asthma or chronic bronchitis: where available, the rate of physician-diagnosed (rather than self-diagnosed) disease is stated. It can be seen that most estimates for the cumulative prevalence of asthma lie between 5% and 10%. The exception is the second study of the population of Busselton, Australia, which reported the prevalence of physician-diagnosed asthma to be 16% (Peat et al. 1992a). This figure is significantly higher than that found in the same population 5 years earlier (Woolcock et al. 1987), suggesting an increase in the prevalence of asthma over this time period. However, the prevalence of bronchial hyper-responsiveness was similar in the two Busselton surveys, and longitudinal surveys in other areas have suggested a much smaller increase in the prevalence of diagnosed asthma (Viegi et al. 1994a). Thus increased awareness of asthma and altered diagnostic practices may have contributed to the very high prevalence of diagnosed asthma in the second Busselton survey (Peat et al. 1992a).

Three of the studies in Table 1.4 give separate figures for the prevalence of asthma in different age groups. Lundback et al reported a higher prevalence of asthma in

Table 1.4: PREVALENCE OF REPORTED DIAGNOSES OF ASTHMA AND CHRONIC BRONCHITIS

PRINCIPAL AUTHOR	PREVALENCE ASTHMA	PREVALENCE BRONCHITIS
Britton 1994	8.0%	
Horsley 1991	8.4%	
Isoaho 1994	7.0% ^m 8.6% ^f	
Krzyzanowski 1990	4.7%	
Lebowitz 1975	9.6%	6.6%
Lundback 1991	5.9%	4.1%
Mortagy 1986	8.2%	
Neukirch 1995	8.0% ^m 6.8% ^f \$	
	9.2% ^m 9.3% ^f \$	
	9.5% ^m 9.2% ^f \$	
Samet 1982*	3.3% ^m 4.8% ^f	3.6% ^m 3.4% ^f
Schachter 1984	7.0% ^m 5.0% ^f	5.0% ^m 3.0% ^f
Trigg 1990	4.9%	
Turkeltaub 1991 [!]	6.9%	1.3%
Viegi 1991 [#]	3.2% ^m 2.8% ^f \$	2.0%
Viegi 1994 [#]	5.2% ^m 3.3% ^f \$	
Viegi 1994 [#]	5.4% ^m 5.5% ^f \$	5.0%
Woolcock 1987**	9.0%	
Peat 1992	16.0%	

\$Grenoble \$\$Montpellier \$\$\$Paris *non-Hispanic population
#employed adults aged 18-64 \$Po River (1) \$\$\$Po river (2) \$\$\$Pisa
**553 subjects aged 19-55 years !whites aged 12-74

older subjects: physician-diagnosed asthma was reported by 6% of subjects aged 65-66, but by only 4%-5% of those aged 35-36 and 50-51 (Lundback et al. 1991). In contrast, two other studies report lower prevalence of self-reported asthma in older age-groups: in Tucson, 7.8% of subjects aged 45-74 and 4.7% aged ≥ 75 reported asthma (Lebowitz et al. 1975), and diagnosed asthma was also inversely correlated with age in French subjects aged 22-45 years in the European Community Respiratory Health survey (Neukirch et al. 1995). These prevalences of self-reported asthma in older adults are all much lower than that described in the preliminary report of a study of 2004 adults aged ≥ 65 years in Sunderland, UK (Parameswaran et al. 1995). In this study, 24.4% of subjects satisfied criteria for a diagnosis of asthma on the basis of a symptoms questionnaire and spirometry. Thus no clear pattern of the effect of age on the prevalence of diagnosed asthma can be found from these studies. Furthermore, differences between age groups in a cross-sectional survey may be the result of changes in disease awareness and diagnostic practices over time; actual changes in disease prevalence with age can only be assessed accurately by a longitudinal study.

Comparisons between prevalence of asthma in different geographical regions are hampered by the different methodology used by different authors. Three studies have compared the prevalence of reported asthma using identical methodology in different regions. Viegi et al compared a rural area of Italy (the Po River Delta) with a more industrial area (Pisa), and also repeated the Po River Delta study after the opening of a large industrial site (Viegi et al. 1991a, 1994a). The prevalence of reported asthma was slightly higher in Pisa than in the first Po Delta study; in the second Po Delta study, this difference was less apparent, suggesting that exposure to environmental pollutants may have been a factor. Secondly, a report from the European Community Respiratory Health Study has compared rates of reported asthma in three French cities, and found significantly lower rates in a city in the Alps (Grenoble) than in Paris. Again, environmental factors were suggested as a cause for this difference (Neukirch et al. 1995). Finally, the second NHANES study in America included a national sample of the population of the United States.

Comparison of diagnoses reported by subjects living in urban and rural areas showed higher prevalence of asthma in rural areas, while allergic rhinitis was reported more commonly in urban areas (Turkeltaub and Gergen, 1991).

The effect of smoking on the prevalence of reported asthma has been assessed by several of the studies summarised in Tables 1.1-1.3. Two studies found similar rates of reported asthma in both smokers and non-smokers (Schachter et al. 1984; Bakke et al. 1990). Furthermore, in one population the number of male smokers aged ≥ 75 reporting asthma was unexpectedly low, raising the possibility of increased mortality in aged male asthmatic smokers (Isoaho et al. 1994b). Evidence for a link between smoking and asthma was reported in a study of twins, where a diagnosis of asthma was found to be more common in those who were smokers (Vesterinen et al. 1988). In the NHANES II study, all upper and lower respiratory conditions were reported more often by smokers, except allergic rhinitis, which was more frequent in non-smokers (Turkeltaub and Gergen, 1991).

In an attempt to characterise subjects reporting diagnosed asthma, some authors have compared them with the rest of the population. In the Tucson study, a reported diagnosis of asthma was associated with increased serum IgE, eosinophil counts, positive skin tests, and reduced FEV₁ (Burrows et al. 1988). Several surveys have shown increased frequency of respiratory symptoms (particularly wheeze and nocturnal breathlessness) in subjects reporting asthma (Mortagy et al. 1986; Lundback et al. 1991; Neukirch et al. 1995). Ethnic differences have also been reported, with diagnosed asthma being more common in non-Hispanic than Hispanic inhabitants of Bernallillo (Samet et al. 1982), and more common in Anglo-Americans than Mexicans (Di Pede et al. 1991).

Few studies have measured the prevalence of chronic bronchitis based on physician diagnosis, perhaps recognising the wide variation in diagnostic practice in this area (Table 1.4). The reported prevalences vary from 1.3% to 7%; this is much lower than the prevalence of chronic bronchitis estimated by other methods (see pages 42,

45). Increasing age and cigarette consumption have been identified as risk factors for a reported diagnosis of chronic bronchitis (Samet et al. 1982; Lundback et al. 1991; Turkeltaub and Gergen, 1991), although in the Tucson study the prevalence of chronic bronchitis was similar for subjects aged younger and older than 75 (Lebowitz et al. 1975).

iii) Estimated prevalence of respiratory symptoms

Several questionnaires have been designed to assess the prevalence of symptoms associated with asthma and chronic bronchitis (van der Lende and Orie 1972; Mortagy et al. 1986; Burney and et al. 1989; Venables et al. 1993). Most of these are adapted from respiratory symptoms questionnaires designed by the Medical Research Council (MRC) (Medical Research Council 1960) or the American Thoracic Society (ATS) (Ferris 1978). However, the symptoms associated with asthma and chronic bronchitis (and indeed emphysema) are similar. The same symptoms are also seen in other respiratory and cardiovascular diseases, and questionnaire data alone may be insufficient to distinguish between these. Evaluation of the sensitivity and specificity of symptoms questionnaires for the identification of asthma or chronic bronchitis is thus important, but problematic in view of the absence of a gold-standard test for the diagnosis of asthma or chronic bronchitis (Toren et al. 1993). Most studies have compared the results of questionnaires with those of bronchial challenge tests or physician examinations.

The results of epidemiological surveys which have estimated the population prevalence of respiratory symptoms are summarised in Table 1.5. It can be seen that the reported cumulative prevalence of the various symptoms vary widely between populations, and in some populations are surprisingly high. Even higher figures are obtained when the prevalence of **any** respiratory symptom is considered: 36.5% of Italian men and 21.2% of women aged 18-64 reported one or more respiratory symptoms (Viegi et al. 1991a), as did 41% of Swedes aged less than 67 years (Lundback et al. 1991), 58.4% and 60% of Britons aged ≥ 65 years (Dow et al.

Table 1.5: PREVALENCE OF RESPIRATORY SYMPTOMS

PRINCIPAL AUTHOR	WHEEZE	COUGH	SPUTUM	DYSPNOEA
Boezen et al 1995	13.6% ^m 11.8% ^f	6.0% ^m 5.3% ^f	6.0% ^m 5.3% ^f	14.0% ^m 17.9% ^{f*}
Broder 1974		21%	17%	10%
Burr 1985	20.3% ^m 15.1% ^{f!}	24% ^m 12% ^{f#}		
Caird 1972		26% ^m 13% ^{f#}		
Dow 1991	28.4%	21.6%		20.6%\$
Horsley 1991	24.2%	16.4%#		38.0%# #
Isoaho 1994		12.5% ^m 6.5% ^{f#}	12.1% ^m 6.5% ^{f\$}	9.3% ^m 7.5% ^{f*}
Krzyzanowski 1990	5.6% ^m 3.3% ^f	18.9% ^m 9.2% ^{f\$}	23.7% ^m 10.1% ^{f\$}	6.2% ^m 23.7% ^{f*}
Lebowitz 1975	11.3% ^m 6% ^f	28% ^m 19% ^f	27.1% ^m 16.6% ^f	14.4% ^m 17.9% ^{f*}
Lundback 1991	14%	10%	22%	11.6%
Menezes 1994		12.7%#		
Milne 1978	12% ^m 7% ^{f!}	37% ^m 16% ^f	42% ^m 15% ^f	4% ^m 10% ^{f*}
Mortagy 1986	25.5%		13.5%\$	29.0%# #
Neukirch 1995	14%			
Rijken 1987	5.4%	12.4%	10.0%	6.5%*
Samet 1982	20.3% ^m 17.1% ^f	14.0% ^m 10.8% ^{f\$}	14.8% ^m 13.2% ^{f\$}	3.3% ^m 8.5% ^{f*}
Schachter 1984	22.0% ^m 20.0% ^f			
Trigg 1990	22.1%	5.5%		28.7%
Viegi 1991!!	18%**	12%\$	10%\$	4%*
Viegi 1991\$\$	8%**	9%\$	9%\$	3%*
Woolcock 1987	17.5%	10.7%\$		6.3%*
Peat 1992	28.8%	13.1%\$		7.8%*

*MRC grade III+ \$daily for 3 months yearly !attack of dyspnoea/wheeze within 1 year \$at rest
#productive daily for 3 months yearly **for 6 months yearly #exertional !!Pisa \$river Po (1)

1991; Horsley et al. 1991), 50% of Dutch adults aged 20-70 (Boezen et al. 1995) and 38.4% of men and 36.5% of women aged 18-70 in Cracow, Poland (Krzyzanowski and Lebowitz 1992).

Most surveys have shown an increase in the prevalence of symptoms with age (Lebowitz et al. 1975; Burr et al. 1979; Mortagy et al. 1986; Rijken et al. 1987; Bakke et al. 1991c; Lundback et al. 1991; Viegi et al. 1991a; Boezen et al. 1995), with this relationship even extending above the age of 65 (Dow et al. 1991). Smoking is also associated with a higher prevalence of respiratory symptoms (Milne and Williamson 1972; Samet et al. 1982; Rijken et al. 1987; Bakke et al. 1991c; Di Pede et al. 1991; Horsley et al. 1991; Lundback et al. 1991; Viegi et al. 1991a; Krzyzanowski and Lebowitz 1992; Menezes et al. 1994). In the Normative Aging Study, current smoking was the strongest predictor of new onset of wheezing over 3 years of follow-up; the risk of developing wheeze also increased with increasing age (Sparrow et al. 1993). Thus, differences between the age range and smoking habits of the various populations studied may explain some of the variation in symptom prevalence.

Exposure to pollution has also been suggested as a factor contributing to the variation in symptom prevalence between urban and rural areas. Several population comparisons have suggested higher symptom prevalence in areas with environmental pollution than in non-polluted areas (Viegi et al. 1991a), with this difference being particularly prominent in non-smokers (Detels et al. 1981; Hodgkin et al. 1984). However, this difference was not confirmed by the European Community Respiratory Health Survey of French cities (Neukirch et al. 1995). Occupational exposure to dusts or gases has also been associated with increased reporting of respiratory symptoms in some populations (Hodgkin et al. 1984; Bakke et al. 1991c; Viegi et al. 1991b). In a study of adults with asthma or chronic bronchitis, frequency of respiratory symptoms increased with increasing levels of ambient air pollution (Higgins et al. 1995). However, studies comparing the prevalences of asthma and atopy in West and East Germany have found higher levels of both in the

affluent West than in the industrial East (Magnussen et al. 1993).

There is some evidence that the reporting of respiratory symptoms is increasing. The two cross-sectional studies of the Busselton population in 1981 and 1990 used the same respiratory symptoms questionnaire: all symptoms were more common in the second survey, particularly wheeze (reported by 17.5% of the population in 1981 and 28.8% in 1990) (Woolcock et al. 1987; Peat et al. 1992a). Barbee et al have reported a much smaller increase in symptoms over 8 years of follow-up of a subset of subjects taking part in the Tucson epidemiological survey: the prevalence of allergic rhinitis increased by 11% in this cohort over 8 years of follow-up (Barbee et al. 1991).

Several population-based surveys have found differences in the respiratory symptoms reported by men and women. Men describe cough, sputum and wheeze more often than women (Caird and Akhtar 1972; Milne and Williamson 1972; Lebowitz et al. 1975; Burr et al. 1979; Krzyzanowski et al. 1990; Bakke et al. 1991c; Viegi et al. 1991a; Isoaho et al. 1994a; Neukirch et al. 1995), whereas breathlessness is more common in women than men (Milne and Williamson 1972; Lebowitz et al. 1975; Krzyzanowski et al. 1990; Bakke et al. 1991c; Viegi et al. 1991a; Isoaho et al. 1994a).

Some authors have compared levels of pulmonary function and bronchial responsiveness in symptomatic and asymptomatic subjects. Symptomatic subjects tend to have lower spirometry results than asymptomatic subjects (Caird and Akhtar 1972; Burr et al. 1979; Krzyzanowski et al. 1990; Isoaho et al. 1994a; Lundback et al. 1994), and in one population, mean FEV₁ progressively decreased with increasing number of symptoms reported (Boezen et al. 1995). Symptomatic subjects also have a higher prevalence of bronchial hyper-responsiveness than asymptomatic subjects (Rijken et al. 1987; Trigg et al. 1990), with increased bronchial responsiveness being more strongly associated with wheeze than cough or sputum (Rijken et al. 1987, 1989; Trigg et al. 1990). Symptoms suggesting "bronchial

irritability" (morning chest tightness for ≥ 1 hour, nocturnal breathlessness, and breathlessness or wheeze triggered by exposure to inhaled irritants) were strongly associated with increased bronchial responsiveness in a population sample of young adults (Mortagy et al. 1986), but not in older adults (Horsley et al. 1991; Dow et al. 1992b).

Comparison of Tables 1.4 and 1.5 shows that the prevalence of respiratory symptoms is higher than the prevalence of diagnosed asthma or chronic bronchitis in most populations. The significance of this is not clear. It may be that subjects completing questionnaires report symptoms which are not of sufficient severity to take them to their doctor. Alternatively, doctors may be failing to make appropriate diagnoses in symptomatic patients, so underestimating the prevalence of respiratory disease. In Tucson, many symptomatic subjects without a diagnosis of asthma or chronic bronchitis went on to receive such a diagnosis in subsequent years (Dodge and Burrows 1980). In contrast, studies including physician examination of all subjects have found that only a small proportion of symptomatic subjects meet diagnostic criteria for asthma or chronic bronchitis (Broder et al. 1974; Cerveri et al. 1987; Lundback et al. 1993a; Murray, SA and Graham 1995). Thus it seems likely that surveys relying on respiratory symptoms questionnaires alone will overestimate the population prevalence of asthma.

Unlike asthma, the definition of chronic bronchitis is based purely on the presence of a particular combination of symptoms (ie chronic cough and sputum production). Consequently, it might be expected that the prevalence of these symptoms would be similar to the prevalence of diagnosed chronic bronchitis. However, as Tables 1.4 and 1.5 show, cough and sputum production are reported far more commonly than a diagnosis of chronic bronchitis. Under-reporting of diagnosed chronic bronchitis by older smokers has been noted in the NHANESI health survey (McWhorter et al. 1989), and this may contribute to the discrepancy between the prevalence of symptoms and diagnoses. However, under-reporting of symptoms has also been described, particularly in older smokers (Lundback et al. 1993a).

iv) Prevalence of chronic airflow obstruction

The inclusion of spirometry in epidemiological surveys gives an objective method of detecting airflow obstruction. Measurement of PEF, FEV₁ and FVC does not require complex equipment, and can be mastered by the majority of adults, including the elderly (Connolly et al. 1988b). However, as asthma is defined in terms of variable airflow obstruction, a single measurement of pulmonary function provides only limited diagnostic information. Repeated measurements on separate occasions (for example by measurement of peak flow variability over a period of time (Higgins et al. 1989b)) will increase the sensitivity of the technique, but are rarely feasible in large population surveys. Furthermore, simple spirometry will not distinguish between asthma, chronic bronchitis, and other causes of chronic airflow obstruction.

For this reason, assessment of response to bronchodilator has been included in some surveys (Burr et al. 1979). However, reversibility of chronic airflow obstruction does not reliably distinguish between asthma and chronic bronchitis (Kesten and Rebeck 1994), and does not show consistent correlation with measurement of bronchial responsiveness (Postma et al. 1988). Asthmatic subjects in remission with normal lung function may not show a bronchodilator response. Moreover, opinions differ on the best way of defining bronchodilator reversibility. Traditionally, a cut-off of 15% increase over baseline FEV₁ has been used to define reversible airflow obstruction - but this fails to take into account short-term variability in repeated lung function measurements, which may approach 15% in subjects with low baseline FEV₁. This has led some authors to define reversibility as an absolute increase, rather than a percentage increase, in expiratory flow volume (Tweeddale et al. 1987).

The prevalence of chronic airflow obstruction in some published cross-sectional population surveys is summarised in table 1.6. In the majority of these studies, spirometry has been performed prior to the start of bronchial challenge in order to identify subjects excluded because of airflow obstruction. Varying definitions of airflow obstruction have been used, making direct comparisons between the different

Table 1.6: PREVALENCE OF CHRONIC AIRFLOW OBSTRUCTION

PRINCIPAL AUTHOR	DEFINITION OF AIRFLOW OBSTRUCTION	PREVALENCE
Britton 1994	%FEV1 < 60% or FEV1 < 1.5l	3.9%
Burney 1987	%FEV1 < 60%	8.2%
Burrows 1987	%FEV1 < 75%	9.8% ^m 11.5% ^f
Cerveri 1988	%FEV1 < 75%	1% 44
Higgins 1988	%FEV1 < 60%	8.2%
Higgins 1993	%FEV1 < 60%	3.8%
Horsley 1993	%FEV1 < 80% or FEV1 < 1l	8.3%
Isoaho 1994	FEV1/FEV% < 65%	12.5% ^m 3.0% ^f
Kryzanowski 1990	%FEV1 < 75%	6.4% ^m 3.3% ^f
Mortagy 1986	%FEV1 < 50% or FEV1 < 1.5l	15.5%
Rijken 1988	%FEV1 < 80%	8%
Trigg 1990	%FEV1 < 70%	3.0%
Woolcock 1987	%FEV1 < 60%	4.4%
Peat 1990	% FEV1 < 65% or FEV1/FVC% < 65%	18.2%

studies difficult. The measured prevalence of chronic airflow obstruction varies widely, from 1% to 18.2%.

Studies comparing lung function in different geographical areas using the same methodology have suggested a relationship with environmental pollution. The UCLA population study compared spirometry results in two different areas of Los Angeles: the prevalence of impaired lung function was higher in a heavily polluted area than in a relatively unpolluted area, but these differences were smaller than the difference between smokers and non-smokers (Detels et al. 1981). In the first NHANES study, a significant negative association was found between measurements of FEV_1 and FVC and levels of total suspended particulates for over 6000 adults aged 25-75 living in 49 cities across the United States (Chestnut et al. 1991). This relationship remained after adjustment for smoking and socio-economic characteristics.

Two of the surveys summarised in Table 1.6 actually set out to estimate the population prevalence of chronic airflow obstruction. Isoaho et al measured the prevalence of "chronic obstructive pulmonary disease" (COPD) in adults aged >64 years in Lieto, Finland, defining COPD as $FEV_1/FVC\% < 65\%$ (Isoaho et al. 1994a). COPD was found in 3% of women and 12.5% of men; the majority had only minimal reversibility following salbutamol inhalation. COPD was more common in smokers: the prevalence in non-smokers was only 2%. Only 51% percent of men and 33% of women with COPD had chronic productive cough, and less than half had a diagnosis of airflow obstruction in their medical records. The authors concluded that chronic airflow obstruction may have an insidious onset and remain asymptomatic until considerable loss of respiratory reserve has occurred, and that there may be a large amount of undiagnosed chronic airflow obstruction in elderly populations. Similar conclusions were reached by a study of Busselton, Australia, where the prevalence of "chronic airflow limitation" (CAL - defined as $FEV_1/FVC\% < 65\%$ or $FEV_1\% < 65\%$ predicted) was found to be 18.2% (Peat et al. 1990). Again, CAL was more common in smokers, and increased with increasing age. Only 45% of subjects with CAL had either persistent cough or

exertional breathlessness.

The fact that many subjects with chronic airflow obstruction do not describe typical symptoms has also been noted in other populations. In Tucson, Burrows separated subjects with airflow obstruction into 3 groups: heavy smokers, those with diagnosed asthma, and others (Burrows 1990, 1991). There was no age difference between the 3 groups. Respiratory symptoms were reported more frequently by the "asthmatic" group than the heavy smokers. This suggests either that smoking-related airflow obstruction produces fewer symptoms than airflow obstruction in asthma, or that the smokers were under-reporting symptoms. The latter has previously been noted in another study (Lundback et al. 1993a).

v) Prevalence of increased bronchial responsiveness

Nonspecific bronchial responsiveness to histamine or methacholine is the best available objective measure of airways lability. In small studies, increased bronchial responsiveness has been shown to be closely related to symptomatic asthma (Cockcroft et al. 1977). Although requiring more complex equipment than measurement of simple spirometry, shortened protocols using portable equipment have been described and used successfully in large epidemiological surveys (Yan et al. 1985; Peat et al. 1992b).

The results of epidemiological surveys of bronchial responsiveness are summarised in Table 1.7. For ease of comparison, PD_{20} results initially reported in micromoles of histamine or methacholine have been converted to micrograms. Different authors have used different parameters to express the results of bronchial challenge: most use the dose or concentration of challenge agent producing 20% fall in FEV_1 (PD_{20} or PC_{20} - see page 19), but bronchial challenges in the Vlagtwedde/Vlaardingen study were stopped after a 10% fall in FEV_1 (PD_{10}) (van der Lende et al. 1973), and Cerveri et al have reported the PD_{15} (Cerveri et al. 1988). Extrapolation of these results to those expected from higher doses of challenge agent is probably unreliable. Conversion of values of PC_{20} to estimated equivalent levels of PD_{20} is

Table 1.7: PREVALENCE OF INCREASED BRONCHIAL RESPONSIVENESS

PRINCIPAL AUTHOR	CHALLENGE AGENT*	DEFINITION OF BRONCHIAL HYPER-RESPONSIVENESS	PREVALENCE (%)
Bakke 1991	M	PC20 < 8mg/ml	6.0
		PC20 < 32mg/ml	20.0
Britton 1994	M	PD20 < 2400µg	13.0
Burney 1987	H	PD20 < 2600µg	14.0
Cerveri 1988	M	PD15 < 4800µg	57.0
		PD15 < 1900µg	5.0
Higgins 1988	M	PD20 < 4700µg	23.0
		PD20 < 2400µg	15.0
		PD20 < 2600µg	10.0
Higgins 1993	M	PD20 < 4800µg	22.3
Horsley 1994	M	PD20 < 200µg	12.0
		PD20 < 1200µg	43.0
Trigg 1990	M	PC20 < 2mg/ml	23.0
		PC20 < 32mg/ml	54.0
van der Lende 1973	H	PC10 < 16mg/ml	17.0
Viegi 1994**	M	PD20 < 1000µg	7.6
		PD20 < 4800µg	25.0
Woolcock 1987	H	PD20 < 1300µg	10.5
Peat 1992	H	PD20 < 1300µg	7.9

*H = Histamine M = Methacholine
**Po River (1)

possible: a PC_{20} of 1mg/ml methacholine is approximately equivalent to a PD_{20} of 100 μ g methacholine (Beach et al. 1993).

Unfortunately, there is no real agreement on what represents a normal bronchial challenge result, and what defines increased bronchial responsiveness. In the recommendations for standardisation of bronchial challenge testing published by the European Respiratory Society (Sterk et al. 1993), it is suggested that $PD_{20} > 1500\mu$ g ($> 7.8\mu$ mol) of histamine or methacholine should be regarded as a normal result, and that levels below this represent abnormally increased bronchial responsiveness. However, the original studies of the relationship between asthma and bronchial responsiveness suggested that this level of bronchial responsiveness had a low positive predictive value for asthma. Cockcroft et al suggested that while $PC_{20} > 8\text{mg/ml}$ methacholine (equivalent to $PD_{20} > 800\mu$ g) made a diagnosis of asthma extremely unlikely, only a $PC_{20} < 1\text{mg/ml}$ ($PD_{20} < 100\mu$ g) gave a positive predictive value approaching 100% (Cockcroft et al. 1985). Thus, while a $PD_{20} < 1500\mu$ g may not be "normal", this is unlikely to be a useful marker for the identification of individuals with asthma in a population survey. Beach et al have proposed that bronchial responsiveness be described as mildly increased if PD_{20} is 100-800 μ g, moderately increased if PD_{20} is 12.5-100 μ g, and greatly increased if $PD_{20} < 12.5\mu$ g. This leaves a large area of measurable but minimally increased responsiveness ($PD_{20} = 800\text{-}6400\mu$ g), the significance of which is unclear (Cockcroft et al. 1977; Beach et al. 1993).

Using these definitions, most studies summarised in table 1.7 are reporting the prevalence of very mildly increased bronchial responsiveness. As expected, these prevalences are higher than those of self-reported asthma (Table 1.4). Few studies have reported the prevalence of levels of bronchial hyper-responsiveness likely to be associated with definite asthma. Bakke et al describe a 6.0% prevalence of $PC_{20} < 8\text{mg/ml}$ in Hordaland (Bakke et al. 1991a); $PD_{20} < 200\mu$ g ($PC_{20} < 2\text{mg/ml}$) was found in 23.0% of the adult population of Surrey, and in 12.0% of those ≥ 65 years in the New Forest (Trigg et al. 1990; Horsley et al. 1993).

Studies including a respiratory symptoms questionnaire as well as bronchial challenge have shown that not all subjects with increased bronchial responsiveness have symptoms suggestive of asthma. For example, over half of the subjects with bronchial hyper-responsiveness ($PC_{10} < 16\text{mg/ml}$) in the Vlagtwedde/Vlaardingen study were asymptomatic; this may partly be a result of the definition of increased bronchial responsiveness used in this study, which would be expected to include a significant number of non-asthmatic individuals (Rijken et al. 1987). Asymptomatic bronchial hyper-responsiveness has also been identified in populations of children (Asher et al. 1988; Pattemore et al. 1990), and in adolescents and young adults (Kolnaar et al. 1995).

The significance of bronchial hyper-responsiveness in asymptomatic subjects is unclear (Cockcroft and Hargreave 1990). It may precede the onset of symptomatic asthma, represent very mild "subclinical" asthma, represent asthma in subjects with a high symptom threshold, or it may not be related to asthma at all. In a study of adults with rhinitis and no symptoms of asthma, a subset were found to have levels of peak flow variability and bronchial hyper-responsiveness typical of asthma (Ramsdale et al. 1985a). The authors suggested that these individuals had "subclinical" asthma, and either were completely unaware of the sensations produced by variable bronchoconstriction, or regarded these as normal. Asthmatics in remission may have persistent bronchial hyper-responsiveness despite being asymptomatic for 2 or more years (Boulet et al. 1994).

An asymptomatic increase in bronchial responsiveness could also be transient: for example, as the result of a viral upper respiratory tract infection (Empey et al. 1976; Trigg et al. 1994), or following allergen exposure. Longitudinal studies of bronchial responsiveness confirm that this varies over time. In the Vlagtwedde/Vlaardingen study, only half of the subjects who performed at least two bronchial challenges had a measurable PC_{10} on all occasions (Rijken et al. 1993b), and two longitudinal surveys have shown seasonal variation in bronchial responsiveness (Britton et al. 1988b; Trigg and Davies 1991; Trigg et al. 1994).

A study assessing recognition of methacholine-induced bronchoconstriction has shed further light on the relationship between respiratory symptoms and bronchial responsiveness (Stenton et al. 1995). Subjects with 20% fall in FEV₁ during bronchial challenge were asked "have you ever felt like this before?", and their responses were then compared with their reports of wheeze, cough or breathlessness on a questionnaire completed before the challenge. Recognition of bronchoconstriction was more frequent in subjects with marked bronchial hyper-responsiveness, but showed no relationship to reported respiratory symptoms, suggesting that responses to respiratory symptoms questionnaires are poor predictors of bronchial hyper-responsiveness. A similar study, comparing recognition of methacholine-induced bronchoconstriction in old and young subjects, found that awareness of bronchoconstriction in the elderly was not related to level of bronchial responsiveness, and was lower than awareness of younger subjects (Connolly et al. 1992a). These results suggest that the relationship between increased bronchial responsiveness and symptoms may be weaker in the elderly than the young. However, published studies have not assessed whether asymptomatic bronchial hyper-responsiveness is more common in the elderly.

Uncertainty about the significance of asymptomatic bronchial responsiveness has led some authors to define asthma as increased bronchial responsiveness plus asthma-like symptoms (Toelle et al. 1992). In a population study of children, this definition identified a group with greater peak flow variability, evidence of atopy, and use of asthma medication than the rest of the population. In the Busselton population, a definition of asthma as bronchial hyper-responsiveness plus wheeze or breathlessness within the last year gave relatively constant prevalences of asthma in 1981 and 1990, despite large increases in the prevalence of wheeze and reported asthma (Woolcock et al. 1987; Peat et al. 1992a).

Difficulties in interpreting bronchial challenge results have been demonstrated by studies including examination by a physician. In one study of adults with asthma-like symptoms but normal spirometry, physician diagnosis and bronchial challenge result

disagreed in 39% of cases (Adelroth et al. 1986). Similarly, in two further studies of adults with respiratory symptoms, bronchial challenge results showed little relationship to physician-predicted probability of bronchial hyper-responsiveness (Dales et al. 1988; Pratter and Irwin 1988). Moreover, in a cross-sectional population survey, increased bronchial responsiveness was found in only 48% of subjects reporting a diagnosis of asthma (Trigg et al. 1990).

However, in most populations the relationship between bronchial hyper-responsiveness and reported asthma has been found to be relatively strong. Two studies of male industrial workers have found increased bronchial responsiveness to be related more strongly to reported asthma than to respiratory symptoms (Dales et al. 1987; Enarson et al. 1987). In one cross-sectional population study, 79% of subjects designated as asthmatic on the basis of a structured interview and spirometry had $PD_{20} \leq 8\text{mg/ml}$ ($\leq 800\mu\text{g}$) methacholine (Lundback et al. 1993b). Furthermore, in a general practice-based study, bronchial hyper-responsiveness was found in 61.5% of those diagnosed as asthmatic by their doctor, but only 27.6% of subjects reporting attacks of breathlessness and wheeze (Murray, SA and Graham 1995).

A further problem with the use of bronchial challenge in population surveys is that of low response rate. The nature of the bronchial challenge technique, and the degree of co-operation involved, have led to response rates lower than 50% in several studies (Table 1.8). Older subjects, smokers, and those with no past history of obstructive airways disease tend to be under-represented (Lebowitz et al. 1975; Burney et al. 1987; Britton et al. 1994a). Moreover, not all of those who do attend are able to perform satisfactory, reproducible spirometry readings, and this may be a particular problem in studies of older populations (Isoaho et al. 1994a).

In the interests of safety, individuals with low pre-challenge FEV_1 (eg $< 60\%$ of predicted), and those with other medical conditions (for example ischaemic heart disease) are often excluded from bronchial challenge with histamine or



methacholine. This further reduces the number of participants in surveys of bronchial responsiveness, and adds another potential source of bias: older individuals may be more likely to be excluded because of poor health (Table 1.8). For all of these reasons, it is important that information is available to determine whether or not those taking part in a population study are a representative sample. Unfortunately, such information is not always included in published reports (Mortagy et al. 1986; Woolcock et al. 1987; Dow et al. 1991).

Table 1.8: RESPONSE RATE IN EPIDEMIOLOGICAL SURVEYS OF BRONCHIAL RESPONSIVENESS

PRINCIPAL AUTHOR	NUMBER ATTENDING FOR CHALLENGE	RESPONSE RATE*	NUMBER EXCLUDED FROM CHALLENGE**
Bakke 1991	512	86%	1.4%
Britton 1994	2644	48%	5.4%
Burney 1987	522	60%	2.0%
Cerveri 1988	654	71%	7.5%
Dow 1991	324	50%	45.0%
Higgins 1988	130	65%	11.0%
Higgins 1993	212	39%	5.6%
Horsley 1993	180	64%	11.0%
Lundback 1991	284	89%	
Mortagy 1986	207	71%	18.0%
Trigg 1990	318	35%	6.6%
van der Lende 1973	1607	84%	
Viegi 1994#	1616	57%	8.2%
Woolcock 1987	922	60%	4.0%
Peat 1992	1028		1.5%

* attenders as % of those invited
** unable to perform spirometry, FEV₁ too low for challenge, or other contra-indication
Po River Delta (2)

D) FACTORS ASSOCIATED WITH INCREASED BRONCHIAL RESPONSIVENESS

Epidemiological surveys have identified possible associations between bronchial responsiveness and various factors, including age, sex, baseline lung function, diagnosed asthma, respiratory symptoms, smoking and measures of atopy. The relationships with respiratory symptoms and diagnosed asthma have been discussed above; the other factors will be considered below.

i) Pre-challenge airways calibre

The relationship between bronchial responsiveness and baseline FEV_1 or FEV_1/FVC ratio in subjects with chronic airflow obstruction has been discussed above (page 10). Correlation between level of bronchial responsiveness and pre-challenge airways calibre has also been seen both in random population samples and in selected samples of non-asthmatic non-smokers (van der Lende et al. 1973; Malo et al. 1983; Taylor et al. 1985b; Burney et al. 1987; Lim et al. 1988; Trigg et al. 1990; Horsley et al. 1993). In studies using multiple regression analysis to identify factors independently associated with bronchial responsiveness, airways calibre (FEV_1 or $FEV_1/FVC\%$) almost invariably shows a strong association (Kennedy et al. 1990; Bakke et al. 1991b; Peat et al. 1991, 1992b; Britton et al. 1994a; Sparrow et al. 1994). This relationship is not only seen in those with airflow obstruction, but has also been found in populations of subjects (including asthmatics) with normal FEV_1 (Rijken et al. 1988; Ulrik 1993; Sparrow et al. 1994).

There are several reasons why bronchial responsiveness may be directly related to airways calibre. Firstly, the custom of expressing bronchial responsiveness in terms of a percentage change in FEV_1 (PD_{20}) incorporates the level of pre-challenge FEV_1 in the calculation of bronchial responsiveness. Secondly, Poiseuille's law states that resistance to gas flow through a tube is inversely related to the fourth power of the radius of the tube (Benson 1975; Holgate et al. 1987). Thus as the airways become narrower, the effect of smooth muscle contraction on airways resistance will increase, and substantial bronchoconstriction may be triggered by a smaller

stimulus: in other words, bronchial responsiveness will increase. Furthermore, chronic airflow obstruction will tend to increase the proportion of an inhaled stimulus that is deposited in the central airways, and so the response to centrally-acting stimuli will be enhanced (O'Connor et al. 1989b). Alternatively, both bronchial responsiveness and FEV₁ may be altered simultaneously by the same disease process. For example, inflammation and oedema of the bronchial wall epithelium will produce a greater decrease in airways calibre for any given degree of smooth muscle contraction, and so will reduce FEV₁ and increase bronchial responsiveness. Finally, it is possible that bronchial hyper-responsiveness itself is a risk factor for the development of chronic airflow obstruction, as suggested by the "Dutch hypothesis" (Orie et al. 1961).

Since some of the other factors thought to affect bronchial responsiveness (age, sex, smoking, atopy) may also be associated with airways calibre, it is particularly important to correct for FEV₁ when investigating the relationship between these and bronchial responsiveness. Failure to do this makes the results of some published surveys difficult to assess.

ii) Age

The relationship between age and bronchial responsiveness has been examined in several population-based studies, with varying results. In some cases, failure to take the baseline FEV₁ level into consideration makes interpretation of results difficult, as FEV₁ is known to decline with age. The age range of the subjects included is also relevant, as there is some suggestion that the relationship may be U-shaped, with higher prevalence of bronchial hyper-responsiveness in very young and very old subjects. In this case, studies including only middle-aged subjects may fail to detect an association.

Four published studies have shown a decrease in levels of non-specific bronchial responsiveness with increasing age. In a random sample of a Norwegian population (age range 18-73 years, 28% aged >55 years), the prevalence of bronchial hyper-

responsiveness fell with increasing age after adjustment for FEV_1 , sex and smoking status (Bakke et al. 1991a). Similarly, in a large population sample from Nottingham (age range 18-70 years, 14.4% >60 years), bronchial hyper-responsiveness was negatively associated with age in a regression analysis which included 3 measures of airways calibre (absolute FEV_1 , FEV_1 % predicted, and FEV_1/FVC %) (Britton et al. 1994a). In the latter study, initial analysis without adjusting for FEV_1 suggested that bronchial hyper-responsiveness was more common with increasing age.

Thirdly, a study of 652 working men (mean age 40 years, upper age limit 65 years) also reported a negative relationship between age and bronchial responsiveness when baseline FEV_1 was included in the regression equation (Kennedy et al. 1990). Finally, bronchial hyper-responsiveness to cold air hyperventilation was more common in children than adults aged <60 years in a study of 90 families (Weiss et al. 1984).

A U-shaped relationship between bronchial responsiveness and age has been suggested by the results of 3 studies. The first 2 of these did not include adjustment for baseline airways calibre, making the results difficult to interpret. An increased prevalence of bronchial hyper-responsiveness over the age of 55 was found in a random population sample of 522 subjects aged 18-64; the increase in bronchial responsiveness in older subjects was seen mainly in smokers (Burney et al. 1987). Secondly, bronchial hyper-responsiveness was found to increase in prevalence over the age of 60 in 148 non-asthmatic, non-atopic, non-smoking subjects aged 5-86 (18 subjects [12%] aged >65 years) (Hopp et al. 1985). Finally, when the results of 5 separate population studies in Australia (4 studies of children and one of adults) were combined, the prevalence of bronchial hyper-responsiveness was highest in children aged <10 years and adults aged >70 years (Peat et al. 1992c).

If it is true that the prevalence of bronchial hyper-responsiveness in adults increases only above a "threshold" age, then studies including few (or no) subjects above this

threshold will fail to detect an increase. The majority of studies showing no association between bronchial responsiveness and age have contained few older subjects (Cerveri et al. 1988; Davis and Byard 1988, 1990; Trigg et al. 1990; Higgins et al. 1992). The first Busselton cohort contained 114 individuals aged >70 years; however, this still represented only 12% of the study population (Woolcock et al. 1987).

Several studies have documented increased prevalence of bronchial hyper-responsiveness in older adults. In the Vlagtwedde/Vlaardingen study, an increase in bronchial responsiveness with age was noted in the initial analysis (van der Lende et al. 1973). The same relationship was reported again in an analysis of cumulative results recorded over 18 years of follow-up, with adjustment for pre-challenge FEV₁ (Rijken et al. 1993a). Information on the number of older individuals included in this study is not available in the published reports. As part of the Normative Aging study, bronchial challenge was performed by 914 healthy non-asthmatic men between 1984-1987 (age range 41-86 years, 110 subjects [12%] aged >70 years). Analysis of results showed an increase in the prevalence of bronchial hyper-responsiveness with older age (Sparrow et al. 1994). However, when adjustment for pre-challenge level of FEV₁ was included, this relationship only remained significant for former smokers.

Two smaller studies of non-asthmatic subjects also showed an increase in the prevalence of bronchial hyper-responsiveness with age. The first of these was a Chinese study of 86 non-asthmatic non-smokers aged 11-68 years (You-ning et al. 1986). The second included 211 subjects aged 22-86, but did not adjust for pre-challenge FEV₁ in the multiple regression analysis (Lang et al. 1987).

In summary, it is not clear whether there is a relationship between bronchial responsiveness and age. The different methods of analysis used in different studies, failure of some authors to include pre-challenge FEV₁ level in regression equations, and small numbers of older adults included in most surveys, have led to conflicting

results in the published literature. Although an increase in bronchial responsiveness as part of the ageing process is biologically plausible (see page 27), there is as yet no firm evidence that this occurs.

iii) Gender

The published evidence for a relationship between bronchial responsiveness and gender is confused. Bronchial hyper-responsiveness has been found by several authors to be equally prevalent in both sexes (Malo et al. 1983; Weiss et al. 1984; Hopp et al. 1985; Burney et al. 1987; Higgins et al. 1993; Britton et al. 1994a). However, other studies have found increased bronchial responsiveness to be more common in women (Rijken et al. 1987; Cerveri et al. 1988; Trigg et al. 1990; Carrozzi et al. 1992; Peat et al. 1992a). Only one study has found it to be more common in men (Bakke et al. 1991a). However, not all authors have included adjustment for pre-challenge FEV₁. In Vlagtwedde/Vlaardingen, initial analysis suggested increased prevalence of bronchial hyper-responsiveness in men (Rijken et al. 1987), but this trend was reversed when FEV₁ was taken into account (Rijken et al. 1993a). Similarly, Britton et al found that a trend for increased bronchial responsiveness in women became insignificant when FEV₁ was included in the regression equation (Britton et al. 1994a). In contrast, in the Lieto population, adjustment for pre-challenge FEV₁ revealed a relationship between increased bronchial responsiveness and male sex which was not apparent from initial analysis of the data (Bakke et al. 1991a).

iv) Smoking

Many studies have suggested a link between smoking and bronchial hyper-responsiveness (Kabiraj et al. 1982; Buczko et al. 1984; Welty et al. 1984; Burney et al. 1987; Sparrow et al. 1987, 1991a; Bakke et al. 1991a; Carrozzi et al. 1992; Peat et al. 1992b; Higgins et al. 1993), but it is not clear whether this is a causal relationship. In the long-term, smoking decreases airways calibre, and so this must be taken into consideration when the effects of smoking on bronchial responsiveness are considered. Thus in some cross-sectional studies, an apparent relationship

between smoking habit and increased bronchial responsiveness has been removed by inclusion of pre-challenge FEV₁ in the analysis (Kennedy et al. 1990; Trigg et al. 1990; Rijken et al. 1993a; Britton et al. 1994a).

Despite this, there is some evidence that smoking increases bronchial responsiveness independently of its effect on FEV₁. Three studies of subjects with normal FEV₁ have found higher bronchial responsiveness in smokers than nonsmokers (Kabiraj et al. 1982; Taylor et al. 1985b; Cerveri et al. 1989). Furthermore, cigarette consumption and FEV₁ were both found to be independently associated with bronchial hyper-responsiveness in a study of smokers undergoing surgery for malignant disease (Mullen et al. 1986). A direct effect of smoking on bronchial responsiveness is plausible: both inflammation and increased permeability of bronchial epithelium have been demonstrated in human smokers, and both are also implicated in the pathogenesis of increased bronchial responsiveness in asthmatics (O'Connor et al. 1989b).

There are several potential sources of bias in research on smoking and bronchial responsiveness. Firstly, since bronchial hyper-responsiveness is associated with respiratory symptoms on exposure to inhaled stimuli, it could in theory reduce tolerance to cigarette smoke (Mortagy et al. 1986). Thus individuals with increased bronchial responsiveness may be more likely to develop symptoms and give up smoking. This has been termed the "healthy smoker effect", and it would be expected to reduce the strength of the relationship between smoking and increased bronchial responsiveness. Secondly, evidence suggests that older smokers have a tendency to deny respiratory symptoms and under-report diagnosed chronic bronchitis in questionnaire surveys, reducing the estimated prevalence of respiratory morbidity in a population (Lundback et al. 1993a). Furthermore, smokers may be reluctant to take part in studies of pulmonary function: the prevalence of smoking in one population survey was 10% lower than the estimated prevalence for the entire population (Britton et al. 1994a). Alternatively, symptomatic smokers concerned about their symptoms may be more likely to take part in respiratory health surveys,

thus falsely increasing the measured prevalence of respiratory symptoms. Such potential sources of bias may explain some of the conflicting results in the literature.

v) Atopy

Early studies of atopic subjects showed a high prevalence of bronchial hyper-responsiveness, with significant correlation between the number of positive skin tests and the level of bronchial responsiveness (Cockcroft et al. 1984). However, further studies in large populations have not produced consistent results. One reason for this may be the use of different measures of atopy, including skin testing, total IgE level and eosinophil count. These different parameters may not measure the same aspects of the atopic process. Indeed, individuals with positive skin tests may have normal IgE level and eosinophil counts (Burrows et al. 1989). Some authors have suggested that there may be different "atopic phenotypes", with different measures of atopy being associated with different atopic manifestations (Tollerud et al. 1991).

The relationships between skin tests, total IgE levels, eosinophil counts and bronchial responsiveness will be discussed below.

a) Skin tests

The results of several population studies confirm that positive skin tests are associated with increased bronchial responsiveness (Burney et al. 1987; Lang et al. 1987; Trigg et al. 1990; Carrozzi et al. 1992; Peat et al. 1992b; Higgins et al. 1993; Britton et al. 1994a). Some authors have noted a reduction in the strength of this relationship with increasing age (Burney et al. 1987; Peat et al. 1992c; Higgins et al. 1993), which may be related to the general decline in skin test positivity seen in older individuals (Hanneuse et al. 1978; Barbee et al. 1987; Cline and Burrows 1989; Tollerud et al. 1991).

No consistent relationship has been found between skin test positivity and smoking status. Current smokers had fewer positive skin tests than never-smokers in the Tucson epidemiological survey (Burrows et al. 1976; Barbee et al. 1987; Cline and

Burrows 1989) but a higher prevalence of positive skin tests than ex-smokers in another study (Welty et al. 1984). In contrast, two studies have found positive skin tests to be more common in ex-smokers than in current- or never-smokers (Taylor et al. 1985b; Barbee et al. 1987). This has led to the suggestion that smoking and a highly atopic disposition may be incompatible, so that atopic individuals may be more likely to give up smoking. If true, this may be another manifestation of the "healthy smoker effect" previously discussed.

There is no evidence of a relationship between skin test positivity and baseline airways calibre (O'Connor et al. 1989b).

b) Eosinophil count

Eosinophil counts decrease with increasing age (Hanneuse et al. 1978), and in some studies have been higher in current smokers (Taylor and Luksza 1987; O'Connor et al. 1989b; Tollerud et al. 1991). Both of these factors complicate studies of the relationship between eosinophil count and bronchial responsiveness.

There have been conflicting reports of the relationship between eosinophil count and baseline FEV₁. A negative association (eosinophilia associated with low FEV₁) has been found in several populations (Kauffman et al. 1986; Taylor and Luksza 1987; Burrows et al. 1988; Frette et al. 1991). However, in one population this relationship was abolished by the exclusion of asthmatic subjects (Burrows et al. 1988). Other studies have found no association between FEV₁ and eosinophil count (O'Connor et al. 1989a; Frette et al. 1991).

Several authors have reported an association between eosinophilia and bronchial hyper-responsiveness (O'Connor et al. 1989a; Rijken et al. 1993a; Sparrow et al. 1994). In one study this relationship was found even in skin-test negative "non-atopic" subjects, suggesting a role for eosinophils in the pathogenesis of bronchial hyper-responsiveness independent of the atopic process (Taylor and Luksza 1987). However, in the Normative Aging Study, exclusion of asthmatic subjects from the

analysis removed the relationship between eosinophils and bronchial responsiveness (Parker et al. 1990). Moreover, no relationship was found between bronchial responsiveness and eosinophil count in a population of working men (Frette et al. 1991).

c) Serum IgE

Like skin test positivity and eosinophil count, total IgE level falls with increasing age (Hanneuse et al. 1978; Barbee et al. 1981). There is definite evidence that serum IgE is increased in smokers, but as yet this finding has not been explained (Vollmer et al. 1986; O'Connor et al. 1989b; Tollerud et al. 1991; Dow et al. 1992a; Taylor et al. 1985a; Jensen et al. 1992). It is possible that smoking may increase the likelihood of allergen sensitisation, although the lack of a definite association between smoking and skin test positivity in cross-sectional population surveys would not support this theory. There is some evidence, however, that sensitisation to occupational allergens is more common in smokers than non-smokers (O'Connor et al. 1989b), and so the raised IgE in smokers could relate to rare antigens not included in standard skin test protocols (Cline and Burrows 1989). Alternatively, components of cigarette smoke may affect various stages of the immune response, including processing of inhaled antigens, or macrophage or lymphocyte function (Casterline 1983).

The nature of the relationship between total IgE level and airways calibre is unclear. Raised IgE has been associated with low pre-challenge FEV_1 or FEV_1/FVC ratio in some studies (Vollmer et al. 1986; Burrows et al. 1988; Annesi et al. 1992; Dow et al. 1992b), but not others (O'Connor et al. 1989a). Reported relationships between IgE and rate of decline of FEV_1 also vary. Accelerated decline in FEV_1 has been found in symptomatic non-atopic smokers with elevated IgE (Jensen et al. 1992), and in non- and ex-smokers with raised IgE in a working male population (Annesi et al. 1992). However, other population studies have failed to confirm this relationship (Vollmer et al. 1986; Parker et al. 1990).

The relationship between serum IgE and bronchial responsiveness is similarly uncertain. In the Normative Aging Study, bronchial hyper-responsiveness was associated with increased IgE levels (O'Connor et al. 1989; Sparrow et al. 1994); this relationship was also found in the Po River Delta population, with multiple regression analysis revealing IgE level as an independent predictor of bronchial responsiveness in subjects with respiratory symptoms (Carrozzi et al. 1992). In a birth cohort of children, bronchial responsiveness was closely linked to serum IgE level even after the exclusion of children with diagnosed asthma or atopy (Sears et al. 1991). However, this association was not seen in either a Norwegian population or in a cohort of working Parisian men (Bakke et al. 1991a; Annesi et al. 1992).

Some authors have suggested an interaction between smoking and atopy in their effects on airways calibre and bronchial responsiveness. In a study of adults aged ≥ 65 years, multiple regression analysis suggested a synergistic effect of IgE and smoking on FEV₁/FVC ratio, so that smokers with high IgE had the greatest degree of airflow obstruction (Dow et al. 1992a). An interaction between smoking and skin test positivity in their effect on bronchial responsiveness was reported by O'Connor et al, who found that current smokers with positive skin tests had significantly higher levels of bronchial responsiveness than non-atopic smokers (O'Connor et al. 1989a). Similarly, in a study of 654 working men, the only factors significantly associated with increased bronchial responsiveness were pre-challenge FEV₁, younger age, and a interaction between skin test positivity and current smoking (Kennedy et al. 1990). However, no such interaction was found in the Busselton cohort (Peat et al. 1992c).

In summary, skin tests, total IgE levels and eosinophil count are not interchangeable as measures of atopy. Skin test positivity is associated with increased bronchial responsiveness, but not with airflow obstruction. Total IgE levels (and possibly also eosinophil counts) are increased in smokers, but the relationships between these parameters and airways calibre or bronchial responsiveness are not clear.

vi) Other factors affecting bronchial responsiveness

There has been considerable interest in the possible contribution of dietary factors to the pathogenesis of asthma, and relationships between bronchial responsiveness and various dietary components have been investigated. The initial observation that mortality from asthma in England and Wales correlated with sales of table salt (Burney 1987), led to the demonstration that urinary sodium excretion was associated with airway responsiveness to histamine (Burney et al. 1986). However, other studies have failed to confirm this relationship (Sparrow et al. 1991b; Britton et al. 1993). Magnesium induces smooth muscle relaxation in vitro and can cause bronchodilatation in vivo; hypomagnesaemia has been found in some individuals with acute asthma. A large population study of bronchial responsiveness and diet found that dietary magnesium intake was independently related to lung function, bronchial responsiveness and self-reported wheezing (Britton et al. 1994b).

With the recent increases in both reported asthma morbidity and the levels of some air pollutants, research has been performed investigating the effects of air pollutants on bronchial responsiveness. Studies of experimental exposure to ambient levels of SO₂, NO₂ and/or smoke have suggested detrimental effects on lung function and increased symptoms in subjects with pre-existing airflow obstruction (Abramson and Voigt 1991; Molfino et al. 1992). Air pollutants could affect bronchial responsiveness either directly, or indirectly via increased response to specific allergens (Devalia et al. 1994; Tunnicliffe et al. 1994). In general, however, epidemiological studies have failed to identify a relationship between air pollution and asthma. For example, asthma seems to be less common in industrial East Germany than in West Germany, although levels of bronchial hyper-responsiveness appear similar in both (Tattersfield 1996). In one cross-sectional population survey, bronchial hyper-responsiveness was more common in ex-smoking men with a history of exposure to dusts, chemicals or gases, but no convincing difference was seen in women (Viegi et al. 1994b).

As smoking becomes less socially acceptable, interest has increased in the effects

of passive exposure to cigarette smoke on health. Although parental smoking has been implicated in the development of respiratory symptoms in children, there is no evidence that passive smoking, at least in the short term, results in impaired lung function or increased bronchial responsiveness (Weiss et al. 1983; Jorres and Magnussen 1992).

Comparisons of levels of bronchial responsiveness in individuals of different ethnic origins have suggested inter-racial differences, although the basis of these differences has not been explained (Pattemore et al. 1989; Sherman et al. 1993).

Chapter 2 : AIMS OF THESIS

- (1) To enlist a representative age-stratified random sample of white adults aged ≥ 45 years (including a large proportion of elderly adults) from the local (Central Manchester) population.
- (2) To measure the population prevalence of reported asthma, bronchitis and respiratory symptoms by postal questionnaire.
- (3) To measure the prevalence of chronic airflow obstruction using spirometry.
- (4) To measure the prevalence of increased bronchial responsiveness by bronchial challenge with methacholine.
- (5) To investigate the relationships between bronchial responsiveness and age, atopy, airways calibre and smoking.
- (6) To assess the effects of chronic airflow obstruction and bronchial hyper-responsiveness on quality of life.
- (7) To assess the effects of bronchial challenge on oxygen saturation.

Chapter 3: EQUIPMENT AND METHODS

A) POPULATION SAMPLING

i) Selection of random population sample

The study aimed to recruit a representative population sample of adults, including large numbers of older subjects (age-stratified random sample). A lower age limit of 45 years was selected because of the hypothesis of a "U-shaped" relationship between age and bronchial responsiveness, with the frequency of bronchial hyper-responsiveness increasing in adults over the age of 55-60 years (Hopp et al. 1985; Burney et al. 1987; Peat et al. 1992c) (see page 55). Non-Caucasian adults were excluded because of suggested inter-racial differences in bronchial responsiveness (Sherman et al. 1993). As the study protocol included completion of a questionnaire and hospital attendance for bronchial challenge, housebound adults and those with significant cognitive impairment were also excluded.

The study was approved by the Central Manchester Health Authority Ethical Committee. Names, addresses and dates of birth of a random sample of adults aged ≥ 45 years and registered with local General Practitioners (GPs) were taken from computerised records of the Central Manchester Family Health Services Authority (FHSA), using computerised generation of random numbers. Three hundred and ninety-five patients of 101 GPs were selected in this way.

GPs were then contacted by post, informing them of the nature of the study and listing patients who had been selected; patients themselves were not contacted until the approval of their GP had been obtained. Twenty-two GPs replied, approving the inclusion of 65 patients in the study. This low response was in part attributable to GP dissatisfaction at the release of patient details by the FHSA without GP consent.

Seven of the 22 GPs responding to the initial letter subsequently agreed to the recruitment of a further sample of their patients. Random number tables were used to select patients from the computerised practice list of each of these GPs. Non-Caucasian names were discarded at this point. A list of selected patients was then

screened by the GP, who identified those excluded from the study, plus any felt to be unsuitable for other reasons (eg psychiatric problems, malignant disease). All other patients were contacted by post (see below).

Patient recruitment continued from December 1991-December 1993. In the last months of recruitment, an increase in the number of older adults in the study population was achieved by discarding the details of every second person selected at random who was aged less than 70 years.

Eligible subjects were sent a short explanatory letter (Appendix 2.1), describing the aims and nature of the project. This was accompanied by a questionnaire and a pre-paid envelope. Letters were printed on notepaper headed with details of the appropriate GP practice, and informed subjects that their GP was aware that they had been contacted. GP headed notepaper was used in an attempt to improve response rates.

The questionnaire (Appendix 1) was designed for this study, and had two purposes: a) to estimate the prevalence of asthma, chronic bronchitis and respiratory symptoms in the population, and to provide information on smoking habits, and b) to identify subjects suitable for bronchial challenge. Exclusion criteria for bronchial challenge were: significant history of ischaemic heart disease (previous myocardial infarction, heart failure, arrhythmias or symptomatic angina) and the use of medications influencing the outcome of bronchial challenge - ie oral steroids, anticholinergic drugs, and oral or topical beta-blockers). Respiratory symptoms questions were adapted from the MRC respiratory symptoms questionnaire (Medical Research Council 1960). The questionnaire was written in simple language, printed in large type, and covered one side only of 5 sheets of paper. An early experiment with questionnaires printed on both sides of the paper revealed that most subjects filled in only one side.

Returned questionnaires were examined, and responses recorded. Incomplete

questionnaire pages were returned to the subject with an explanatory note and a pre-paid envelope. Subjects not excluded from bronchial challenge by the criteria listed above were contacted by telephone and invited to attend hospital on one occasion for bronchial challenge. A suitable date was arranged, and the subject was requested to refrain from caffeine-containing drinks for 12 hours before this. Those taking bronchodilators were requested to omit these for 12 hours (inhaled preparations), 24 hours (oral medications) or 48 hours (sustained release preparations) before attending. All potential attenders were asked if they had a recent upper respiratory tract infection, or an exacerbation of wheezing: hospital attendance was delayed for 6 weeks after any such episode.

A confirmatory letter (Appendix 2.4) was sent to all subjects who had made an appointment, reminding them of these instructions and the appointment time, and requesting them to inform us if they would be unable to attend or developed an upper respiratory tract infection. A map of the hospital was also included. Suitable subjects who could not be contacted by telephone were allocated an appointment and sent the confirmatory letter by post.

Subjects who failed to attend were contacted by telephone with the aim of arranging another appointment, and answering any worries which may have led to non-attendance. Non-attenders who could not be contacted by telephone were sent a letter requesting that they indicate whether or not they wished to be sent a further appointment. Subjects defaulting twice were not sent further appointments.

ii) Non-responder tracing

Subjects who failed to return the first questionnaire were sent a reminder letter and second copy of the questionnaire after approximately 4-6 weeks. The reminder letter incorporated an "opt-out" slip, allowing the subject to request not to be sent an appointment for bronchial challenge (Appendix 2.2). This was intended to maximise the response rate, so that subjects who did not wish to attend hospital would feel able to return the questionnaire.

A second reminder letter was sent to subjects failing to respond to the first reminder after one month. This contained an abbreviated version of the questionnaire (Appendix 2.3), and stated that no further participation in the project would be required if the questionnaire was returned. There was also a request to return the letter if the addressee was no longer living at that address.

The abbreviated questionnaire was designed to fit onto one page and contain only simple questions, to encourage a response from subjects deterred by the length and complexity of the original questionnaire. To this end, the respiratory symptoms questions were omitted.

A list of persistent non-responders was returned to each GP, who checked to see whether they had recently moved away or died. A random sample of those thought still to be living locally was then contacted by telephone or home visit, and asked to complete the abbreviated questionnaire.

B) ATTENDANCE FOR BRONCHIAL CHALLENGE

All subjects signed an information/consent form, listing the procedures involved, and the possible side-effects of methacholine inhalation (wheeze, headache, facial flushing) (Appendix 3).

A 12-lead ECG was performed; subjects with ECG evidence of ischaemia were excluded from methacholine challenge. A venous blood sample was taken for measurement of serum sodium (Na), potassium (K), magnesium (Mg) levels, differential white cell count, and total immunoglobulin E (IgE) level.

The subject was then taught how to perform spirometry, and baseline pulmonary function was measured (mean of 6 recordings reproducible within 10%). Subjects with baseline $FEV_1 < 60\%$ predicted were excluded from bronchial challenge, but had bronchodilator reversibility measured as described below. A few subjects unable to perform reproducible spirometry manoeuvres were also excluded from bronchial challenge. The challenge technique is described below.

Three questionnaires were completed during the hospital visit. The first of these was an interview-administered questionnaire containing items omitted from the postal questionnaire for reasons of brevity, including questions about symptoms of "bronchial irritability" (Mortagy et al. 1986), symptoms of chronic bronchitis (Medical Research Council 1960), and occupational exposure (Appendix 4). Secondly, subjects completed the St George's Respiratory Questionnaire (Jones et al. 1992), which aims to measure quality of life in people with obstructive airways disease (see chapter 15).

For subjects completing the whole methacholine challenge (ie inhaling the maximal dose of methacholine), the entire hospital visit lasted approximately 90 minutes.

i) Bronchial challenge technique

a) Preparation of methacholine solutions

Crystalline methacholine chloride (Sigma pharmaceuticals) was stored at -20°C in a desiccator until use. A stock solution of 64 mg/ml methacholine in 0.4% phenol (BDH Chemicals Ltd, Blyth) was prepared using distilled water; sequential dilutions were made on a daily basis using a diluent of 0.5% sodium bicarbonate in 0.4% phenol. Both the stock solution and the diluent were suction filtered through a $0.22\text{ }\mu\text{m}$ millipore membrane filter (Nalgene) to remove any particulate matter, rendering the solutions effectively sterile. Solutions were protected from light at 4°C until use, and replaced every 3 months (Pratter et al. 1982).

Doubling dilutions of methacholine chloride solution ($3.125\mu\text{g/ml}$ - $3200\mu\text{g/ml}$) were prepared daily from the stock solution and diluent. The alkaline diluent was necessary to neutralise the natural acidity of methacholine in solution; the use of unbuffered acidic solutions of histamine for bronchial challenge has been shown to produce a slight enhancement of bronchial responsiveness at low levels of pH (ie pH < 5) (Cockcroft and Berscheid 1982). Phenol was included as a preservative. The pH of all methacholine dilutions was tested with a pH meter: pH ranged from 6.99 ($3200\mu\text{g/ml}$) to 8.42 ($3.125\mu\text{g/ml}$).

Twelve nebulisers were calibrated as described below, and numbered 1-12. Nebuliser 1 contained 3ml of sterile normal saline; aliquots of 3ml of increasing doubling dilutions of methacholine solution were placed in nebulisers 2-12. As nebuliser output is temperature dependent, solutions were allowed to warm to room temperature prior to use. Each nebuliser was activated for 3 seconds before the start of the first challenge, to ensure that all internal surfaces were wetted with nebulised solution.

b) Function of Newcastle dosimeter

The Newcastle dosimeter is an electronic timing device, designed to allow activation of a series of nebulisers for precise periods of time, to ensure accurate output of

nebulised solution. It is controlled by a microprocessor, and triggering of nebuliser activation at the start of each inhalation can be produced either manually, or automatically by a pressure transducer. For the purposes of this study, the dosimeter was triggered manually by the operator at the start of each inspiration, as it had been observed that some older subjects were "startled" by automatic triggering.

Triggering of the dosimeter opens a valve for a exact time period, the length of which is controlled by the micro-processor program. While the valve is open, compressed air passes from a compressed air cylinder to the nebuliser; a pressure gauge (Budenberg Gauge Co Ltd, Cheshire) attached to the dosimeter allows the compressed air pressure to be maintained at 20 lb/in². Nebulisation ceases when the valve is closed; residual compressed air escapes via a venting device so that nebulisation ceases immediately. The nebuliser is supported on a height-adjustable retort stand.

The microprocessor program not only controls the time for which each nebuliser is activated, but also displays the current dose and inhalation number throughout the challenge. The program delivers 5 inhalations from each nebuliser, following which the nebuliser is removed from the retort stand, and replaced by the nebuliser containing the next doubling concentration of methacholine.

c) Measurement of lung function

For the Newcastle dosimeter technique, the mean of 6 measurements of FEV₁ is usually recorded prior to the inhalation of each dose of methacholine (Hendrick et al. 1986). To avoid fatigue in elderly patients, reproducible challenge results have also been obtained using the mean of 3 FEV₁ measurements (Connolly et al. 1988b).

For the purposes of this study, 3 reproducible recordings of FEV₁ and PEFR were made immediately before inhalation of each methacholine dose. FEF₅₀ was recorded for the first of each 3 blows (repeated measurements of FEF₅₀ were not made, as this parameter is known to be particularly affected by repeated forced expiration).

Reproducibility of all spirometry measurements was $\pm 10\%$. The use of a computer-controlled spirometer (Compact, Vitalograph, Buckingham) allowed FEV₁, PEFR and FEF₅₀ to be calculated from a single maximal forced expiration. Challenge results were calculated using both the mean and the maximum measurement of each of these parameters; the repeatability of these results is compared in chapter 5. All readings were made in the seated position, with the subject wearing a nose-clip. The spirometer was calibrated daily.

d) Monitoring of oxygen saturation

Studies of oxygenation during bronchial challenge in asthmatic subjects have suggested that some subjects may experience relative hypoxia during the procedure (Fontana et al. 1993). All subjects undergoing bronchial challenge as part of the current study had oxygen saturation and pulse rate monitored using a finger oximeter (Biox 3700e, Ohmeda, Louisville, USA). Because pulse rate and oxygen saturation were observed to increase following spirometry, all readings were taken immediately before each set of spirometry manoeuvres.

e) Inhalation of methacholine

Following 6 reproducible baseline spirometry readings, the subject inhaled nebulised saline from the mouthpiece of the first nebuliser. Five inspiratory capacity breaths, each lasting for 5 seconds (with breath-holding at total lung capacity), were taken from the nebuliser mouthpiece (Hendrick et al. 1986). The dosimeter was triggered at the start of each inhalation by the test operator, activating the nebuliser for the exact period of time (usually 1.0-2.5 seconds) required to give an output of 10 μ l of solution. A total of 50 μ l of nebulised solution was thus inhaled during the 5 capacity breaths. At the end of 5 seconds the dosimeter produced an audible tone, signalling that inhalation/breath-holding could cease. Subjects were encouraged to delay as little as possible between the 5 inhalations.

Five minutes after the start of the first inhalation of saline, pulse rate and oxygen saturation were recorded, and the subject then performed three spirometry

manoeuvres before inhaling the lowest dose of nebulised methacholine (again delivered as five x five second inhalations). The test then continued in 5 minute cycles: at the beginning of each five minute period, pulse rate and oxygen saturation were recorded; the subject then performed three spirometry manoeuvres, followed by inhalation of the next dose of methacholine. The subject then rested until the end of the next five minutes, when the whole procedure would be repeated. The test continued until either the final dose of methacholine had been inhaled, or the subject developed bronchoconstriction sufficient to produce a 20% fall from the baseline FEV₁.

At the end of the test, all subjects who had experienced a 20% fall in FEV₁ were given 1mg of inhaled terbutaline (Bricanyl, Astra Pharmaceuticals, Herts) via a metered dose inhaler and plastic spacer device (Nebuhaler, Astra Pharmaceuticals). Subjects remained within the department until FEV₁ had increased to within 10% of the baseline value. All nebulisers were emptied and washed carefully in warm soapy water. To ensure the adequacy of this cleaning technique, swabs were taken from all nebulisers; culture of these revealed no evidence of bacterial or fungal contamination.

iii) Measurement of bronchodilator reversibility

Subjects with baseline FEV₁ <60% predicted did not undergo methacholine challenge, but instead had assessment of bronchodilator reversibility. Inhaled terbutaline (1mg) was given via a metered dose inhaler and plastic spacer device, and spirometry was repeated after 10 minutes. To allow for variability in spirometry recordings (which can be marked in subjects with low lung volumes), reversibility was expressed in terms of a fixed volume increase in response to bronchodilator, rather than a percentage increase (Tweedale et al. 1987). Thus, significant reversibility was recorded if baseline FEV₁ increased by 160ml following terbutaline inhalation.

C) CALIBRATION OF NEBULISER OUTPUT

The Newcastle dosimeter method relies on knowledge of the precise output of each individual nebuliser ($\mu\text{l}/\text{sec}$) to allow calculation of the exact time period for which the nebuliser must be activated to nebulise $10\mu\text{l}$ of solution per inhalation. These timings are then included in the microprocessor program controlling the dosimeter.

Traditionally, nebuliser output has been measured in terms of weight loss, with the nebuliser being weighed before and after activation for a specific time period. However, this method assumes that all fluid lost from the nebuliser during activation is the result of nebulisation, whereas in fact there is also simultaneous loss of solvent as a result of evaporation (Cockcroft et al. 1989). This evaporative loss leads to cooling and concentration of the solution in the nebuliser reservoir; consequently, measurement of weight loss will lead to over-estimation of solute output. A more accurate method of nebuliser calibration involves direct measurement of output using a chemical (fluoride) tracer impacted onto filter papers (Dennis et al. 1990).

i) Calibration method

A solution of 1.0% sodium fluoride (BDH Chemicals Ltd, Blyth) was prepared in distilled water. Aliquots of 3ml of this solution were placed in each nebuliser reservoir (Turret Turbo nebulisers, Medic-Aid, Pagham, W. Sussex) using a pipette (Pressmatic, Bibby). Before the start of the calibration procedure, each nebuliser was activated for 2 seconds to ensure that all internal surfaces were wet. A 47mm glass fibre filter (Whatman GF/A; BDH Chemicals Ltd) held in a plastic holder (In-line filter holder; Nalgene) was then attached 5cm from the nebuliser outlet via a rubber connector (Vacuum gasket, Nalgene). To maximise impaction of solute onto the filter, and to simulate the effect of inhalation by the subject, a suction pump (N035.1.2AN.18; KNF Neuberger UK Ltd, Oxon) was used to draw ambient air through the filter paper and nebuliser outlet at 200mbar suction pressure. The posterior outlet of the nebuliser was occluded during calibration.

The dosimeter micro-processor was programmed to activate each nebuliser for 5 separate periods of 2 seconds, using compressed air at a pressure of 20 lb/in². The suction pump was switched on throughout each 2-second activation. After 5 x 2-second activations, the filter was removed and placed in a Universal container containing 20 ml of a 50% solution of total ionic strength adjustment buffer (TISAB; BDH Chemicals Ltd) in distilled water. The container was then sealed and left for at least 12 hours at room temperature to allow the fluoride to desorb.

Fluoride analysis was performed using a fluoride-specific ion electrode (Dennis et al. 1990). A pH/ion meter (Delta 255, Ciba Corning Analytical, Halstead) fitted with a fluoride-specific ion electrode and double junction reference electrode plus an automatic temperature-compensation probe (Premium Electrodes, Ciba Corning Analytical, Halstead) was calibrated using reference solutions of sodium fluoride. These were prepared by adding known volumes of 1.0% sodium fluoride solution to 20ml aliquots of 50% TISAB buffer in Universal containers.

Nebuliser output was expected to be approximately 5 μ l/s (ie 10 μ l per 2-second activation), thus each filter paper was estimated to contain approximately 5 x 10 μ l of 1% fluoride solution following 5 x 2-second nebuliser activations. Consequently, two-point calibration of the ion meter was established with reference solutions containing 10 μ l and 100 μ l of 1% sodium fluoride in 20ml buffer; a further reference solution containing 50 μ l of 1% fluoride was used to check the accuracy of the calibration curve. The error of fluoride analysis was within the range $\pm 5\%$. All solutions were agitated continually during analysis using an electromagnetic stirrer. Calibration was re-tested after each 10 readings to maintain accuracy within $\pm 5\%$.

The buffer solutions containing nebulised fluoride desorbed from the glass-fibre filters were then analysed using the same calibration curve. The ion meter reading for each of these solutions represented the volume of 1.0% fluoride solution (μ l) which had desorbed into the buffer solution, that is, the output of each nebuliser during 5 x 2-second activations.

To assess the variability of nebuliser output, the calibration procedure was repeated 3 times for each nebuliser. The mean output ($\mu\text{l}/\text{sec}$) and output variability were calculated: nebulisers with mean output $<4\mu\text{l}/\text{sec}$ or $>8\mu\text{l}/\text{sec}$, or with output variation $\geq 5\%$ were discarded. Suitable nebulisers were numbered, and the activation time producing an output of $10\mu\text{l}$ was entered into the dosimeter micro-processor program for each nebuliser.

Nebuliser calibration was repeated at 6-month intervals using this technique; nebulisers with mean output or variability falling outside the limits defined above were replaced. The results of repeat nebuliser calibration are given in Appendix 5.

ii) Adaptation of calibration technique

Initial nebuliser calibration was performed by the author in Newcastle, under the instruction of J. Dennis, who devised and described this method. Twenty-four nebulisers were tested, 19 of which were found to have acceptable output and variability. Twelve of these were selected for use in the methacholine challenge protocol (Table 3.1).

Calibration of the 12 nebulisers used for methacholine challenge was repeated at 6 month intervals in Manchester, using similar apparatus. Initial results using the Manchester apparatus suggested wide variability of nebuliser outputs, despite all nebulisers previously having had variability $\leq 5\%$ on initial calibration (Table 3.1). Nebuliser outputs were also lower than initially calculated. Possible reasons for this increase in output variability were thought to be: (1) loss of fluoride solution during calibration procedure due to maximal saturation of filter papers; (2) alteration in nebuliser output resulting from cooling of the fluoride solution during repeated activation of the nebuliser; or (3) incomplete impaction of fluoride onto filter because of insufficient suction pressure.

To further investigate these hypotheses, the calibration procedure was repeated using a single nebuliser, which had high variability in output. The following changes were

Table 3.1: calibration of 12 nebulisers

Nebuliser number	Output (μ l/sec) at 0 months	Variability (%) at 0 months	Output (μ l/sec) at 6 months	Variability (%) at 6 months
1	5.25	2	3.6	10
2	4.83	0	4.16	17
3	5.40	0.5	4.63	18
4	5.32	1	3.75	24
5	5.22	2	4.73	23
6	5.23	1	4.04	17
7	5.81	3	4.11	7
8	5.27	2	4.05	20
9	4.79	1	4.34	18
10	5.29	2	3.28	4
11	5.71	1	3.78	2
12	4.29	3	4.38	23

made to the calibration method: (1) two filter papers were inserted simultaneously into the filter-holder, and the fluoride content of each analysed either separately or together; (2) the level of suction applied to the filter paper and nebuliser output was increased to 250 mbar; (3) the fluoride solution in the nebuliser reservoir was changed after each 5 x 2-second activations (Table 3.2).

When 2 filter papers were used, small amounts of fluoride were detected in the filter paper positioned furthest from the nebuliser outlet, suggesting that use of only one filter would lead to incomplete collection of nebulised fluoride. Output variability was reduced when 2 filters were used instead of 1. In contrast, increasing suction pressure and changing fluoride solution more frequently did not markedly improve variability. Thus subsequent calibration was performed as originally described, but using 2 filters in the filter holder and analysing the fluoride content of both simultaneously.

Table 3.2: Effect of alterations to calibration method

Method adjustment*	Mean output ($\mu\text{l/sec}$)	Variability (%)
None	5.41	11
Filter 1 of 2	5.39	10
Filter 2 of 2	0.09	6
Filters 1 + 2	5.50	4
Increased suction	5.37	8
Frequent solution change	5.12	9

*Details in text

D) STATISTICAL ANALYSIS

Data was stored on and analysed by a microprocessor statistics program (Ecstatic, SomeWare in Vermont, USA). Where necessary, log transformation was used to achieve normal distribution. Comparison of sub-groups was performed by grouped t test and χ^2 tables. Multiple regression analysis was used to assess inter-relationships between various parameters. In all cases significance was defined at the 5% level.

Smoking history was expressed as number of packyears smoked, where 1 packyear = 20 cigarettes per day for 1 year.

Further details of certain aspects of data analysis are included in the relevant chapters.

**Chapter 4: QUESTIONNAIRE RESPONSE AND ATTENDANCE FOR
BRONCHIAL CHALLENGE; VALIDATION OF QUESTIONNAIRE**

i) Questionnaire response rate

Of 1025 names selected from GP lists and screened by GPs, 132 (12.8%) met exclusion criteria or were thought to be unsuitable. Twenty-eight of these subjects (21.3%) were housebound, 14 (10.7%) were confused, 13 (9.8%) had psychiatric conditions, 5 (3.8%) had medical conditions precluding participation, 3 (2.2%) did not speak English, and 3 had other reasons for non-inclusion. In the remaining 66 (50.0%), the reason for exclusion was not specified by the GP (this resulted from 2 GPs labelling excluded subjects as "unfit" or "unsuitable" without giving details; the proportion of these subjects meeting agreed exclusion criteria is thus not clear). These 132 subjects were not further included in the study. Questionnaires were sent to 893 subjects, 110 of whom were subsequently excluded: 78 no longer lived locally, 15 had died, 6 were non-Caucasian, 2 housebound, 3 cognitively impaired, 1 deaf-and-dumb, and 5 with other illnesses precluding participation. Mean age of the 110 excluded subjects was 63.3 years; 46 (41.8%) were women. Mean age of the eligible study population ($n=783$) was 66.1 years; 446 (57.2%) were women.

Full questionnaires were returned by 508 subjects (64.9% of the eligible population). Abbreviated questionnaires were returned by 170 subjects, plus 18 visited at home and 27 contacted by telephone: total number of completed abbreviated questionnaires was 215. Questionnaire data was thus available for 723 subjects (92.3% of the eligible population; 81.0% of the 893 subjects initially contacted). Twenty-nine subjects refused to complete a questionnaire.

Subjects contacted at home by telephone or home visit comprised a random sample of persistent non-responders. Thirty phone-calls were made: 27 subjects completed the abbreviated questionnaire, 1 refused, and 2 had moved away before the start of the study. Fifty visits were attempted: 18 subjects completed the abbreviated questionnaire, 1 refused, 10 had moved prior to the study, 3 had moved during the study (regarded as persistent non-responders), there was no reply at 15 addresses, and a further 3 addresses could not be located. This left a total of 31 persistent non-responders (4.0% of the eligible population), of mean age 58.5 years, 17 (54.8%)

of whom were women.

Of the 723 subjects returning a questionnaire, 47.7% responded to the first contact, 22.5% to the first reminder, 23.5% to the second reminder (abbreviated questionnaire), and 6.2% were contacted by telephone or visit.

ii) Demographic details and smoking habits of responders

Table 4.1 compares responders and non-responders. The proportion of women was similar in all subject groups. However, subjects refusing to participate were older than questionnaire responders ($t=2.8$, $p=0.005$), whereas persistent non-responders and non-responders contacted at home were younger than responders (persistent non-responders: $t=-4.0$, $p=0.0001$; non-responders contacted at home: $t=-3.2$, $p=0.001$). The 723 questionnaire responders were representative of the entire study population in terms of age and sex distribution. 1991 Census data suggest that 53% of the local population aged ≥ 45 are women (Office of Population Censuses and Surveys 1991a). Figure 4.1 shows the age distribution of all questionnaire responders: 292 were aged <65 years and 431 ≥ 65 years; 411 were women and 312 men.

Details of smoking habits and history of ischaemic heart disease were available for all subjects completing a questionnaire (Table 4.2). Almost one third (29.2%) of the population were current smokers; a further third (37.3%) were ex-smokers. Table 4.3 shows differences in smoking habit between men and women, and between older and younger adults. Women were less likely to be ex- and current-smokers than men ($\chi^2=54.7$; $p<0.001$); older adults were more likely to be ex-smokers and less likely to be current smokers than younger adults ($\chi^2=13.9$, $p=0.001$).

Younger women were more likely to be current smokers and less likely to be ex- or never-smokers than older women (women <65 years: 39.1% never-smokers,

Table 4.1: Demographic details of responders and non-responders

	Subject number	Mean age (SD)	% women
Entire population	783	66.1 (11.3)	57.2
All questionnaire responders	723	66.7 (11.3)	56.8
Full questionnaire	508	66.6 (11.3)	58.7
Abbreviated questionnaire	215	66.9 (11.3)	52.6
Refused	29	72.5 (11.7)	69.0
Nonresponders contacted by phone or visit	45	61.3 (11.9)	48.9
Persistent non-responders	31	58.5 (11.1)	54.8

Table 4.2: Prevalence of ischaemic heart disease and smoking habit in all questionnaire responders

	number completing question	number (%) of positive responses
Ischaemic heart disease	720	113 (15.7)
Current smoker	719	210 (29.2)
Ex-smoker	713	266 (37.3)

Figure 4.1: Age distribution of questionnaire responders

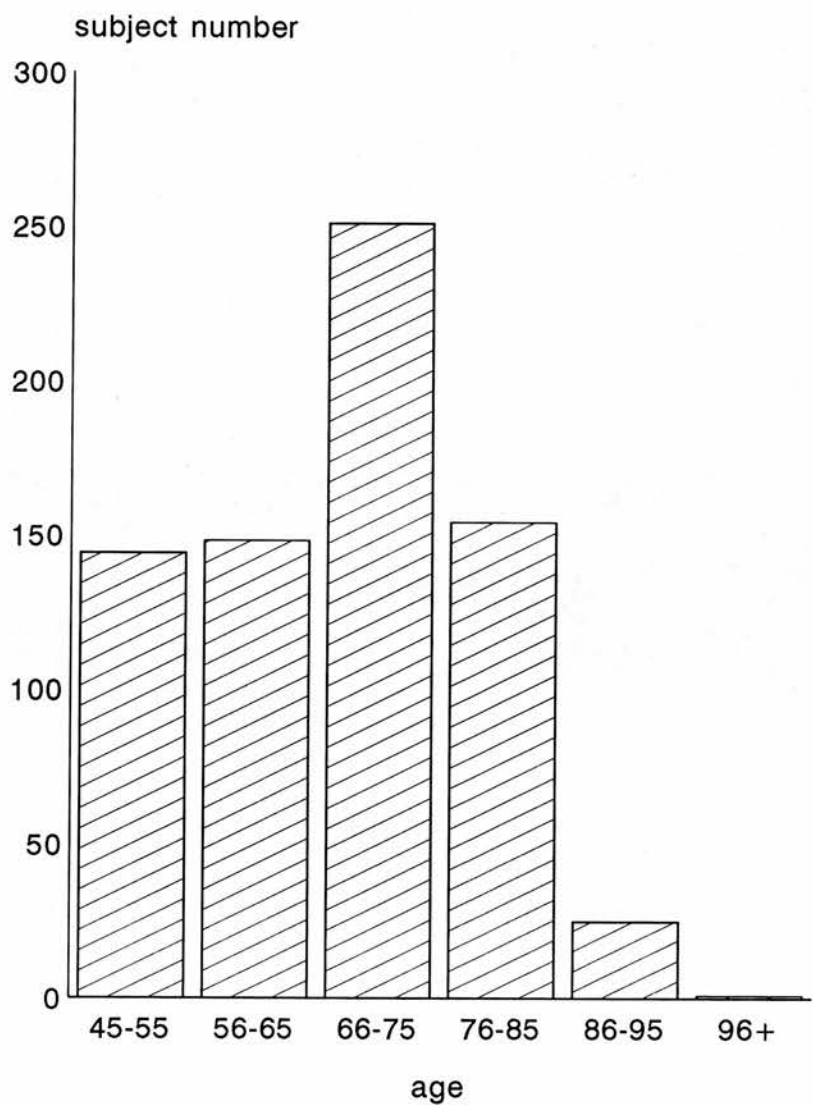


Table 4.3: Differences in smoking habit between sexes and age-groups

smoking status	all women	all men	age <65	age ≥65
never	182 (44.6%)	58 (18.8%)	88 (30.5%)	152 (35.6%)
ex	118 (28.9%)	148 (48.1%)	94 (32.5%)	172 (40.3%)
current	108 (26.5%)	102 (33.1%)	107 (37.0%)	103 (24.1%)

Table 4.4: Comparison of attenders with non-attenders

	Attenders (n=247)	Non-attenders (n=476)	Study population (n=783)	p value*
Age	64.5	67.8	66.1	p<0.05
% women	56.3	57.0	57.2	p>0.1
Current smoker(%)	33.6	30.7	29.2#	p>0.1
Ex-smoker(%)	38.5	36.8	37.3#	p>0.7

* attenders vs non-attenders or study population # questionnaire responders (n=723)

contrast, smoking habits were similar in younger and older men, (men <65 years: 21.0% never-smokers, 40.6% ex-smokers, 38.4% current smokers; men aged ≥65 years: 17.1% never-smokers, 54.1% ex-smokers, 28.8% current smokers, $\chi^2=5.6$, $p=0.06$).

Twenty-six men smoked cigars, pipe tobacco or roll-up cigarettes rather than commercial cigarettes: 16 were current smokers, and 10 ex-smokers.

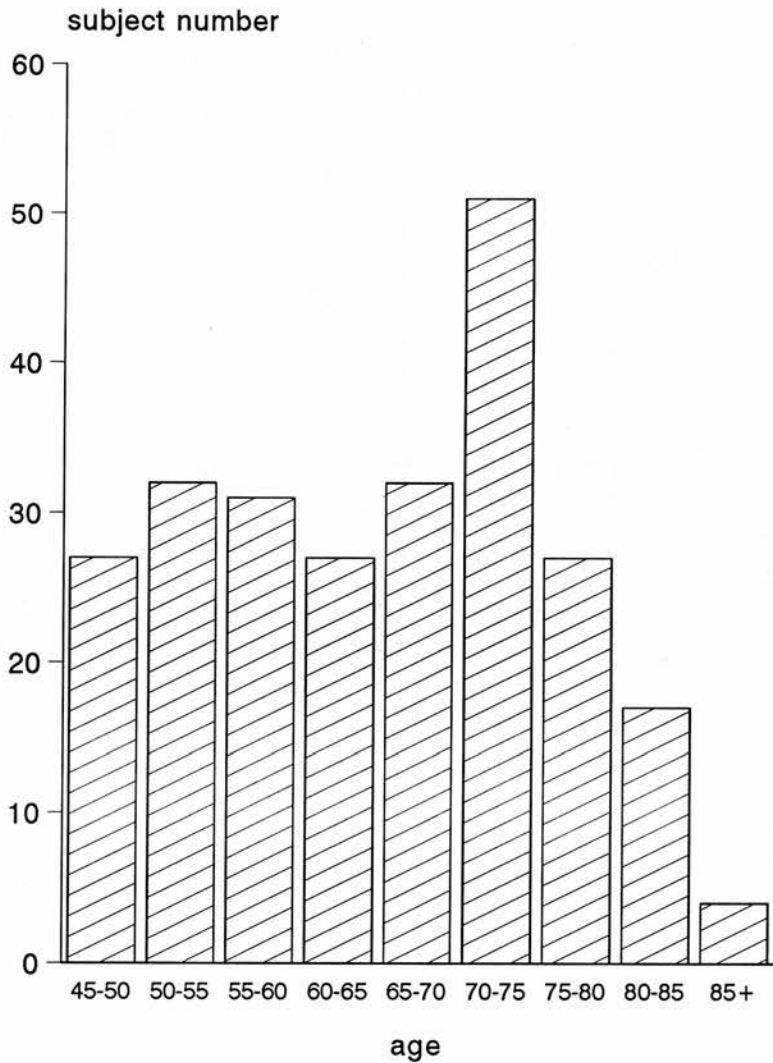
There was no difference between smoking habits of subjects completing full and abbreviated questionnaires. However, non-responders contacted by telephone or home visit had a higher prevalence of current smoking than other questionnaire responders (20.0% never-smokers, 24.4% ex-smokers and 55.6% current smokers; $\chi^2=16.0$, $p<0.001$).

iii) Attendance for methacholine challenge

Of 508 subjects returning the full questionnaire, 113 were excluded from bronchial challenge: 101 reported ischaemic heart disease and/or were using beta-antagonist medications, one was using anticholinergic medication, and 11 oral steroids. The remaining 395 were invited to attend; 247 did so (62.5% of those invited; 31.5% of entire study population). Attenders were significantly younger than non-attenders, but were otherwise representative of the study population (Table 4.4). The age distribution of attenders is shown in figure 4.2: 117 were aged <65 years and 129 ≥65 years; 139 were women and 107 men.

Satisfactory spirometry results were recorded for 246 of the 247 adults attending for bronchial challenge: one woman was unable to perform reproducible spirometry. Twenty-nine attenders did not attempt bronchial challenge: two had ECG evidence of ischaemia, one declined, and baseline FEV₁ was <60% predicted in 26 (the latter had reversibility tested with inhaled terbutaline). Of the 217 subjects attempting the challenge, 9 failed (excessive coughing in 4, fatigue in 3, 1 developed a "choking" sensation, and 1 failed to master the inhalation technique). Full challenge results

Figure 4.2: Age distribution of attenders



were thus available for 208 subjects (118 [56.7%] women, mean age 63.7 years [SD 10.8]).

Side effects were reported by several subjects completing bronchial challenge: the majority of these were minor sensations of flushing and headache, as previously reported (Sterk et al. 1993; Carratala et al. 1995). One woman reported dysphonia after completing a second challenge; both ENT and speech therapy assessment failed to identify a cause for this, and it seemed unlikely to be the result of methacholine inhalation. A second subject was reported by her GP to have developed oral thrush following a challenge: samples of all challenge solutions and swabs from nebulisers and dosimeter were examined by microscopy and culture for bacteria and fungi, with negative results in all cases.

iv) **Validation of postal questionnaire**

Because some of the questions included in the interview-administered questionnaire (completed by subjects attending for bronchial challenge) were similar to those in the postal questionnaire, validation of the latter was possible.

Two questionnaires were completed by 244 subjects. Postal responses about wheeze and sputum were incomplete in 2 cases (Table 4.5). Agreement between the 2 sets of responses was calculated using Cohen's kappa statistic, which adjusts observed agreement with agreement occurring by chance (Cohen, 1960).

Adjustment was made for differences in terminology between the questionnaires. The postal questionnaire asked "does your chest ever sound wheezy", whereas the supplementary questionnaire also asked about wheeze on exertion, with chest infections or on exposure to environmental triggers. For the purposes of questionnaire validation, subjects with wheeze occurring only following exertion/infections/environmental triggers were regarded as "not wheezy". Similarly, subjects reporting breathlessness only on exertion (walking uphill) on the postal questionnaire, or only after exertion/infections/environmental triggers on the

supplementary questionnaire were regarded as "not breathless".

One or more symptoms were reported by 126 subjects on the postal questionnaire, compared with 114 at interview. There was highly significant agreement between questionnaires (sputum: $k=0.645$, $p<0.001$; wheeze: $k=0.460$, $p<0.001$; breathlessness: $k=0.216$, $p<0.001$; any symptom: $k=0.622$, $p<0.001$).

TABLE 4.5 Comparison of symptoms reported on postal questionnaire and at interview

Symptom	Interview	Postal questionnaire symptom absent	Postal questionnaire symptom present
Breathlessness*	Absent	207	9
	Present	22	6
Sputum	Absent	133	20
	Present	20	69
Wheeze**	Absent	136	12
	Present	46	48
Any	Absent	100	29
	Present	17	97

*Not including breathlessness on exertion or with infections

**Not including wheeze on exertion or with infections

CHAPTER 5: REPEATABILITY OF METHACHOLINE CHALLENGE

i) Introduction

Before assessing the influence of different factors on bronchial responsiveness, it is necessary to demonstrate that our method of measuring bronchial responsiveness is repeatable.

Repeatability is best assessed by calculation of the coefficient of repeatability (CR) (Bland and Altman 1986). This then allows calculation of 95% limits of agreement between which further repeated measurements would be expected to lie. This method is more appropriate than that of regression analysis or calculation of correlation coefficients, which have been used by some authors in this context (Juniper et al. 1978), for the following reasons. Correlation assesses the relationship between two readings rather than agreement between them, thus the correlation between two measurements of the same parameter by the same method will always be strong. For perfect agreement between two sets of measurements, the results must lie along the line of identity, and not just along any straight line. Furthermore, the correlation coefficient is influenced by the range of variation between the readings being compared: for a given level of agreement the correlation coefficient will increase with the variance between the two sets of readings (Bland and Altman 1986; Chinn 1991).

For the purposes of this study, repeatability of bronchial challenge was assessed in subjects taking part in the epidemiological survey, and compared with a group of younger volunteers. The results were used to ascertain the most repeatable method of calculating PD_{20} or DRS from spirometry measurements made during the challenge, and also to compare different pulmonary function parameters.

ii) Methods

All subjects completing bronchial challenge were invited to attend for a second time on a separate day. Twenty-one agreed to do so (age 54-84 years [mean 68.3 years, SD 7.4]; 10 women; reported asthma 4; reported bronchitis 4; current smokers 8; ex-smokers 12). A group of young volunteers was recruited from hospital staff

(n=19; age 24-35 [mean age 27.1 years, SD 3.14]; 7 women; reported asthma 4; ex-smokers 3; current smokers 0).

Repeat methacholine challenge was performed in all cases at the same time of day (within 1 hour) as the first challenge, although there is little evidence to suggest a significant diurnal variation in bronchial responsiveness during the daylight hours (Beach et al. 1995). The interval between challenges was 3-10 days, to minimise the effects of refractoriness (demonstrated up to 24 hours following a methacholine challenge) (Beach et al. 1995) and other factors affecting long-term variability, for example viral infection (Empey et al. 1976). No subject reported the development of upper respiratory tract symptoms between the two tests.

iii) Data analysis

Results of the bronchial challenge were expressed as $PD_{20}(FEV_1)$ and $DRS(FEV_1)$. Each of these parameters was calculated twice, firstly using the mean, and secondly the best of the 3 FEV_1 manoeuvres performed after each dose of methacholine. Further calculations of dose-response slope were made using measurements of FEF_{50} ($DRS[FEF_{50}]$), and $PEFR$ ($DRS[PEFR]$). All values for PD_{20} and DRS were log transformed prior to further analysis.

Assessment of repeatability was performed as described by Bland and Altman (Bland and Altman 1986). Graphs of the ratio between the two log measurements of bronchial responsiveness (day 1/day 2) (equivalent to the difference between the measurements on a linear scale) plotted against the geometric mean of the two measurements (ie the nearest estimate of the true value) were used to look for evidence of heteroscedasticity (that is, a relationship between repeatability and level of bronchial responsiveness).

Geometric mean values for DRS or PD_{20} for day 1 and day 2 were compared by paired t test. Coefficient of repeatability (CR) was calculated from the within subject standard deviation using the equation $CR = (2s)$, where $s = \sqrt{(\sum d_i^2/n)}$, d_i = the

difference in paired values of $\log PD_{20}$ or $\log DRS$ for the i^{th} subject, and n = number of subjects. The higher the value of CR, the poorer the repeatability. Approximate 95% limits of agreement for the result of the second of a further pair of measurements were derived from the coefficient of repeatability (lower limit = $1/(\text{antilog CR}) \times \text{first measurement}$, upper limit = $(\text{antilog CR}) \times \text{first measurement}$).

To allow assessment of the effects of age on repeatability, CR was also calculated separately for the 19 subjects aged less than 45 and the 21 subjects aged over 45.

iv) Results

Twenty-two of the 40 subjects had a measurable PD_{20} on both occasions, and 7 on one occasion only. Results of bronchial challenge on day 1 and day 2 are listed in Appendix 6. Comparison of results obtained using the mean or the best of 3 FEV_1 recordings to calculate PD_{20} and DRS revealed superior repeatability using the mean (Table 5.1). Because of this, all subsequent analyses used the mean of 3 spirometry results.

Paired t test revealed no significant difference between the geometric mean reading on the two days for either $PD_{20}(FEV_1)$ or DRS calculated using FEV_1 , FEF_{50} or PEFr (table 5.2). A graph of $DRS(FEV_1)$ on day 1 against day 2 showed strong correlation between the two readings (figure 5.1).

Table 5.3 shows values of the coefficient of repeatability for $PD_{20}(FEV_1)$ and for DRS calculated using FEV_1 , FEF_{50} or PEFr. Maximum repeatability was achieved by expressing bronchial responsiveness as PD_{20} rather than DRS, although the number of individuals with two values for PD_{20} was smaller. Further calculation of PD_{20} inserting a fixed value of $6450\mu g$ for subjects with $PD_{20} > 6400\mu g$ gave a similar result ($CR=0.21$). Both PEFr and FEF_{50} were found to give less repeatable bronchial challenge results than FEV_1 (table 5.3).

Table 5.1: Coefficient of repeatability for PD₂₀ and DRS using mean or best of 3 FEV1 measurements

	Coefficient of repeatability (CR)	95% limits of agreement
PD20# (mean)	0.20	0.40 - 2.48 x initial reading
(best of 3)	0.23	0.35 - 2.82 x initial reading
DRS* (mean)	0.24	0.33 - 3.07 x initial reading
(best of 3)	0.31	0.24 - 4.10 x initial reading

*n=40

#n=22

Table 5.2: Geometric mean values (95% limits of agreement) for PD₂₀(FEV₁), DRS(FEV₁), DRS(FEF₅₀) and DRS(PEFR) on days 1&2

	Day 1	Day 2	Paired t test
PD20(FEV1)	132.28 (48.79-358.67)	176.68 (63.34-492.72)	t=0.23, p=0.82
DRS(FEV1)	29.58 (10.89-71.96)	30.23 (12.04-75.94)	t=-0.86, p=0.39
DRS(FEF50)	51.59 (21.56-123.45)	52.30 (22.24-122.97)	t=-0.15, p=0.89
DRS(PEFR)	32.11 (12.65-81.53)	28.99 (11.81-71.12)	t=-0.94, p=0.35

Figure 5.1: Dose-response slope for day 1 vs day 2
(calculated using mean of 3 FEV1 readings)

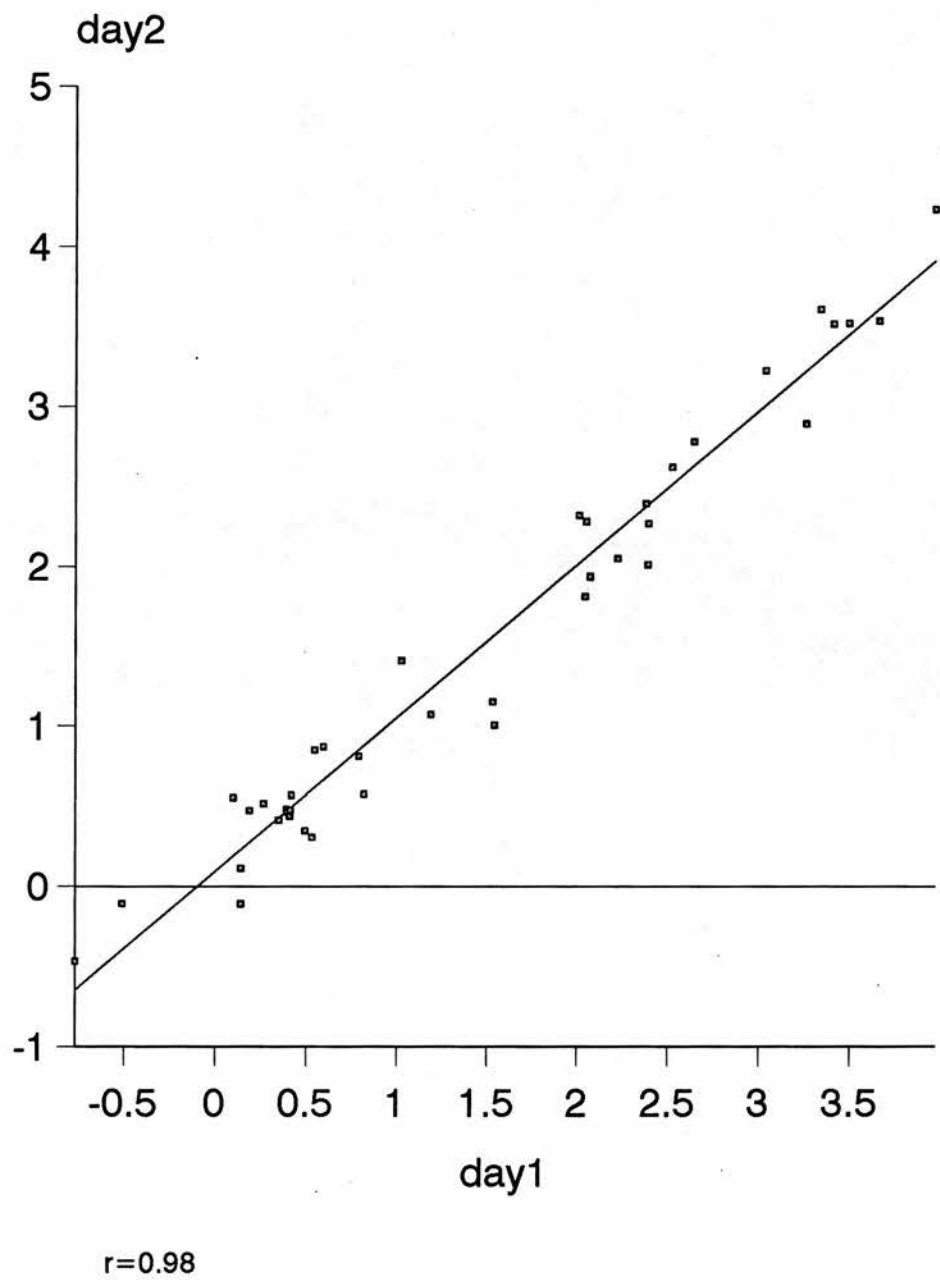


Table 5.3: Repeatability of methacholine challenge using different measures of airway calibre

	Coefficient of repeatability	95% limits of agreement
PD(FEV1)	0.20	0.40 - 2.48 x initial reading
DRS (FEV1)	0.24	0.33 - 3.07 x initial reading
DRS (FEF50)	0.26	0.31 - 3.25 x initial reading
DRS (PEFR)	0.31	0.24 - 4.23 x initial reading

Table 5.4: Repeatability of methacholine challenge in older and younger subjects

	Coefficient of repeatability (95% limits of agreement)	
	AGE <45	AGE >45
PD20 (FEV1)	0.15* (0.50-2.00 x initial reading)	0.21# (0.37-2.68 x initial reading)
DRS (FEV1)	0.21 (0.38-2.66 x initial reading)	0.27 (0.29-3.46 x initial reading)
DRS (FEF50)	0.16 (0.47-2.11 x initial reading)	0.34 (0.21-4.7 x initial reading)
DRS (PEFR)	0.28 (0.37-2.69 x initial reading)	0.33 (0.28-3.56 x initial reading)

*n=6
#n=16

The graph of ratio against mean for $\log \text{DRS}(\text{FEV}_1)$ on the two days shows increasing variability of results at lower values of DRS, implying poorer repeatability at lower levels of bronchial responsiveness (figure 5.2). A similar trend is not seen in the graph of ratio against mean for $\log \text{PD}_{20}(\text{FEV}_1)$, although this graph contains data from fewer subjects (figure 5.3). To further investigate this apparent difference in repeatability of $\text{DRS}(\text{FEV}_1)$ between subjects with high and low bronchial responsiveness, CR was calculated separately for the group of 22 subjects achieving a PD_{20} on both occasions and the 18 subjects with one or no PD_{20} measurements. Coefficient of repeatability was higher in subjects with one or no PD_{20} readings ($\text{CR}=0.26$) than in those with two PD_{20} readings ($\text{CR}=0.23$), confirming that repeatability of DRS was poorer for subjects with lower levels of bronchial responsiveness.

Table 5.4 compares the values of CR for the two age groups. Reproducibility was better for all parameters in the younger volunteers than in the older random population sample, the difference being particularly marked for $\text{DRS}(\text{FEF}_{50})$. Measurements of $\text{PD}_{20}(\text{FEV}_1)$ for subjects taking part in the epidemiological survey were repeatable within 2 doubling doses of methacholine ($\text{CR}=0.21$).

Figure 5.2: Geometric mean DRS(FEV_1) vs ratio of log DRS(FEV_1) for days 1 & 2

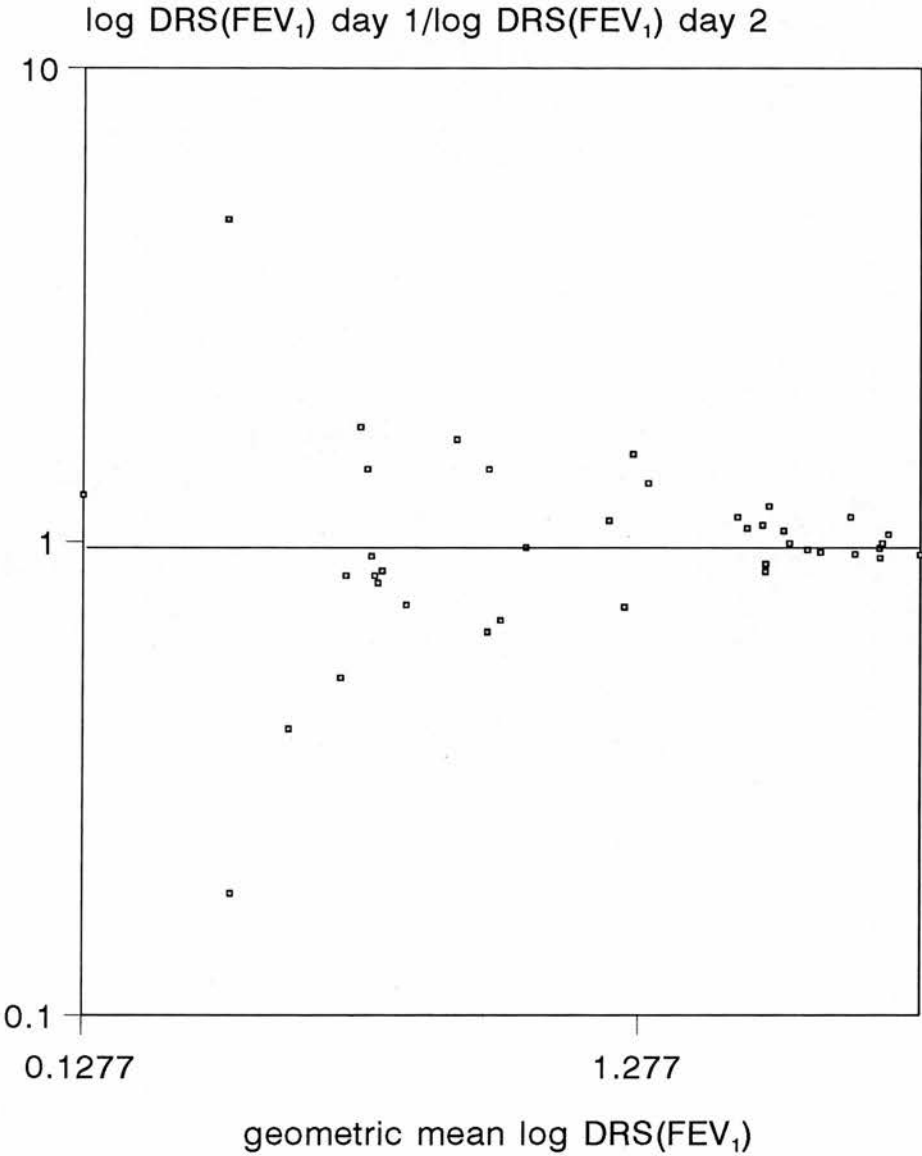
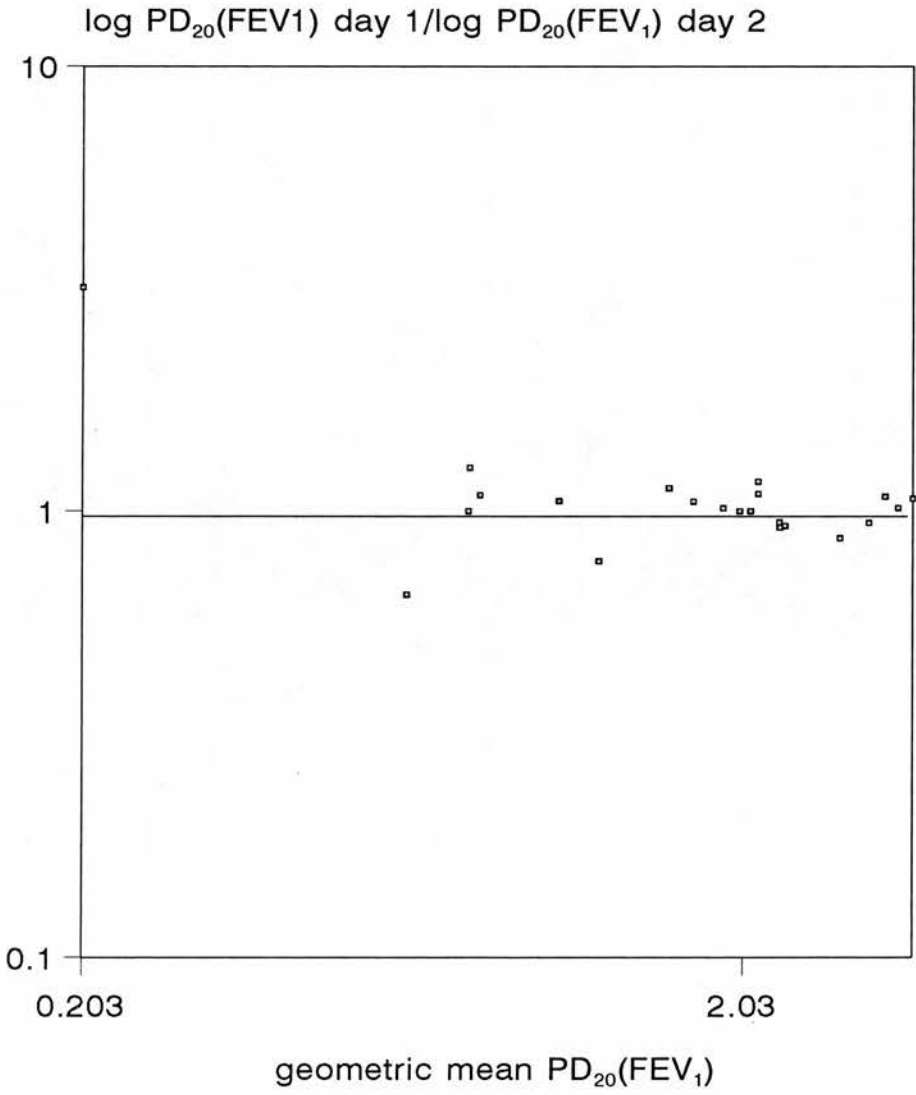


Figure 5.3: Geometric mean $PD_{20}(FEV_1)$ vs ratio of $\log PD_{20}(FEV_1)$ for days 1 & 2



Chapter 6: PREVALENCE OF SELF-REPORTED ASTHMA AND
BRONCHITIS

All 723 subjects completing full or abbreviated questionnaires answered the questions "have you ever been treated for asthma?" and "have you ever been treated for bronchitis?". One hundred and six (14.7%) reported treatment for asthma, and 164 (22.7%) treatment for bronchitis. However, 53 (32.3% of those with bronchitis; 50.0% of those with asthma) reported both asthma **and** bronchitis. Regarding these separately gives prevalence of asthma 7.3%, bronchitis 15.4%, and asthma **plus** bronchitis 7.3%. Only 10 subjects reported treatment for emphysema, 2 of whom also reported bronchitis, and a further 3 asthma plus bronchitis.

Table 6.1 compares reporting of asthma and bronchitis by subjects completing full and abbreviated questionnaires, the 45 non-responders contacted at home, and attenders and non-attenders. Subjects with asthma were over-represented, and those with bronchitis under-represented in the group completing the full questionnaire. Similarly, the group of non-responders contacted at home contained fewer asthmatics and slightly more bronchitics than other responders, although these differences did not reach significance. However, asthma and bronchitis were equally common in attenders and non-attenders.

More women reported a diagnosis: 137/411 women (33.3%) and 80/312 men (25.6%) reported asthma, bronchitis or both diagnoses ($\chi^2=5.0$, $p=0.03$) (Figure 6.1). Women and men had similar prevalences of asthma alone or bronchitis alone (asthma: $\chi^2=0.7$, $p=0.4$; bronchitis: $\chi^2=0.1$, $p=0.7$), but the combination of asthma plus bronchitis was reported more commonly by women ($\chi^2=9.8$, $p=0.002$) (Figure 6.1).

Prevalences of reported asthma and bronchitis were similar in adults aged <65 and those aged ≥ 65 years (Figure 6.2).

Figure 6.3 summarises smoking habits of subjects reporting asthma and bronchitis. Asthma was reported less often by current smokers than ex- or never-smokers ($\chi^2=12.1$, $p<0.001$). In contrast, bronchitis was reported more often by current

Table 6.1: Prevalence of reported asthma and bronchitis
in different responder groups

	n	asthma %	bronchitis %	asthma/bronchitis %	p
All responders	723	7.3	15.4	7.3	
Full questionnaire	508	9.1	14.3	6.6	0.02
Abbreviated	215	2.9	18.0	9.2	
Non-responders*	45	2.2	17.7	11.1	>0.05
Other responders	678	7.7	15.2	7.1	
Attenders	247	8.5	16.7	6.9	>0.05
Non	476	6.7	14.7	7.5	

* contacted at home by phone or visit

Figure 6.1: Prevalence of reported asthma and bronchitis
in women and men

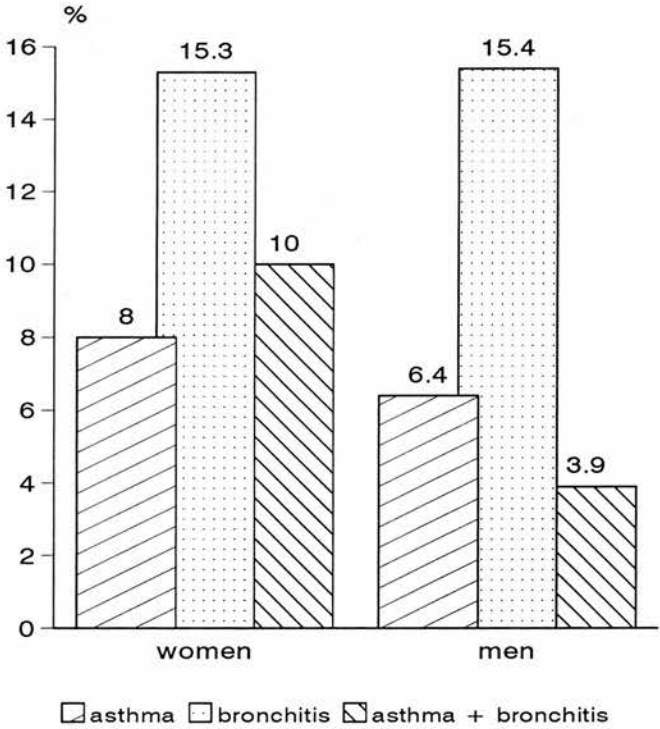


Figure 6.2: Prevalence of reported asthma and bronchitis in older and younger adults

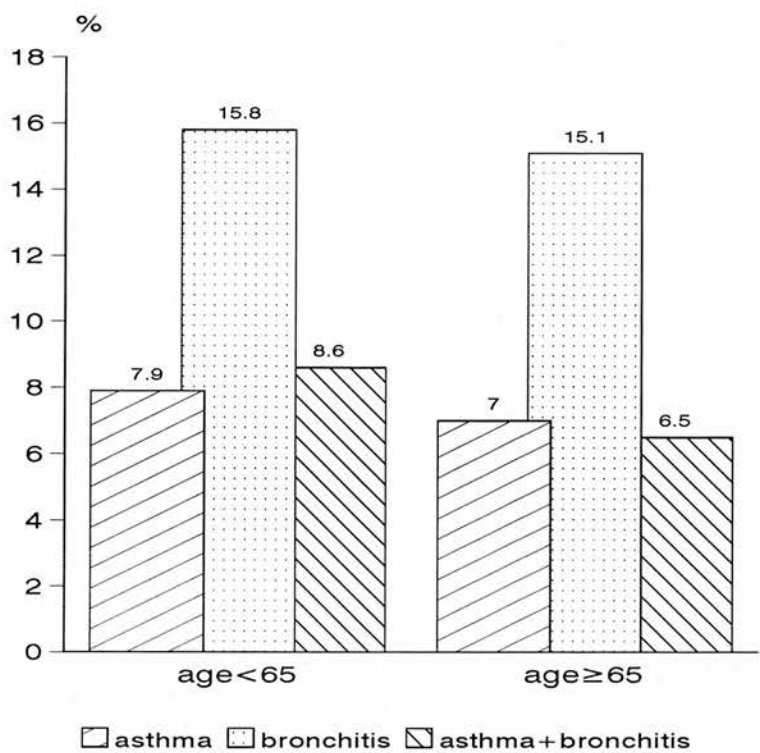
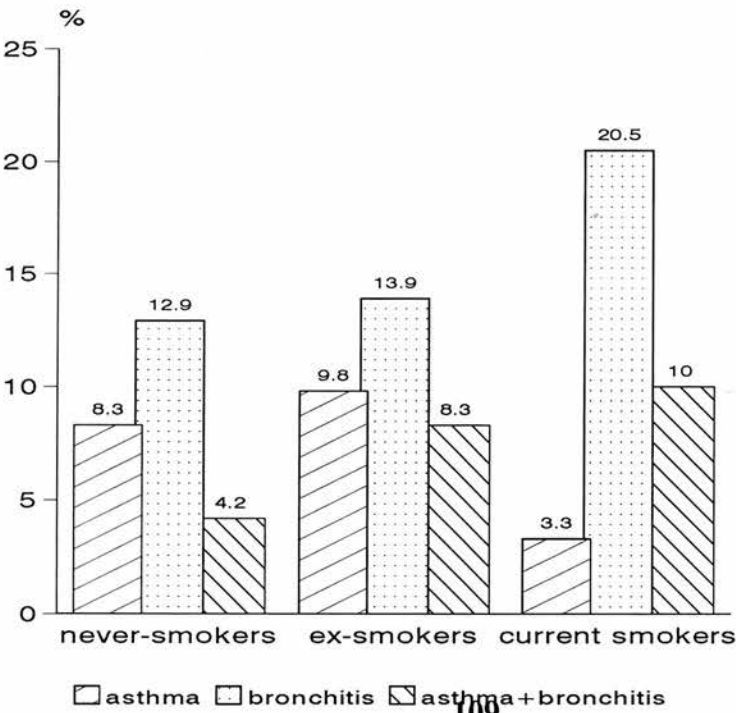


Figure 6.3: Prevalence of reported asthma and bronchitis in current, ex- and never-smokers



smokers ($\chi^2=3.7$, $p=0.05$). The combination of asthma plus bronchitis appeared less common in never-smokers, but this difference was not significant ($\chi^2=3.0$, $p=0.08$). Only 13.2% of those reporting asthma were current smokers, compared with 38.7% of those reporting bronchitis and 39.6% of those with asthma/bronchitis.

Of the 26 subjects smoking cigars or tobacco rather than cigarettes, 2 (7.7%) reported asthma plus bronchitis, and three (11.5%) bronchitis alone.

Chapter 7: PREVALENCE OF RESPIRATORY SYMPTOMS

Information on respiratory symptoms (cough, sputum, wheeze and breathlessness) was available from the 508 full questionnaires. Wheeze was reported by 178/496 subjects (35.9%), cough by 160/496 (32.3%); sputum production by 166/494 (33.6%); and 90/502 (17.9%) reported breathlessness at rest or walking on the level (MRC grade 3+). A further 192 (38%) subjects described breathlessness walking uphill: interpretation of this response was difficult because of standardisation problems ("how steep is the hill?"). Thus, these were regarded as asymptomatic for the remainder of the analysis. By this definition, 53.8% of subjects had respiratory symptoms. Eighty-six (17.5%) reported 1 symptom, 74 (15.1%) 2 symptoms, 71 (14.5%) 3 symptoms, and 33 (6.7%) all 4 symptoms.

The 247 attenders completing the supplementary questionnaire were asked about symptoms suggesting "bronchial irritability" (see pages 41-2) (Mortagy et al. 1986). Breathlessness or wheeze on exposure to respiratory irritants was reported by 104 (42.4%), morning wheeze by 43 (17.6%) and nocturnal breathlessness by 18 (7.3%); 9 subjects (3.7%) reported all 3 of these symptoms. Fifty-one (20.7%) of the subjects completing the supplementary questionnaire had symptoms compatible with chronic bronchitis (Medical Research Council 1960). There was no difference in the proportion of attenders and non-attenders reporting one or more symptoms (attenders: 57.1%, non-attenders 50.8%; $p=0.2$).

Figure 7.1 shows symptoms reported by women and men. Sputum production was more common in men ($\chi^2=18.2$, $p<0.001$), and women reported more breathlessness ($\chi^2=4.0$, $p=0.05$). There was no difference between the sexes in the mean number of symptoms reported (women: 1.1 symptoms, men: 1.3; $t=-1.9$, $p=0.06$). Of subjects attending for bronchial challenge, 21/138 women (15.2%) and 30/107 men (28.0%) described symptoms compatible with chronic bronchitis ($\chi^2=6.0$, $p=0.01$). Symptoms of bronchial irritability were reported equally by men and women.

Figure 7.2 shows symptoms reported by older and younger subjects. There was no

Figure 7.1: Respiratory symptoms reported by women and men

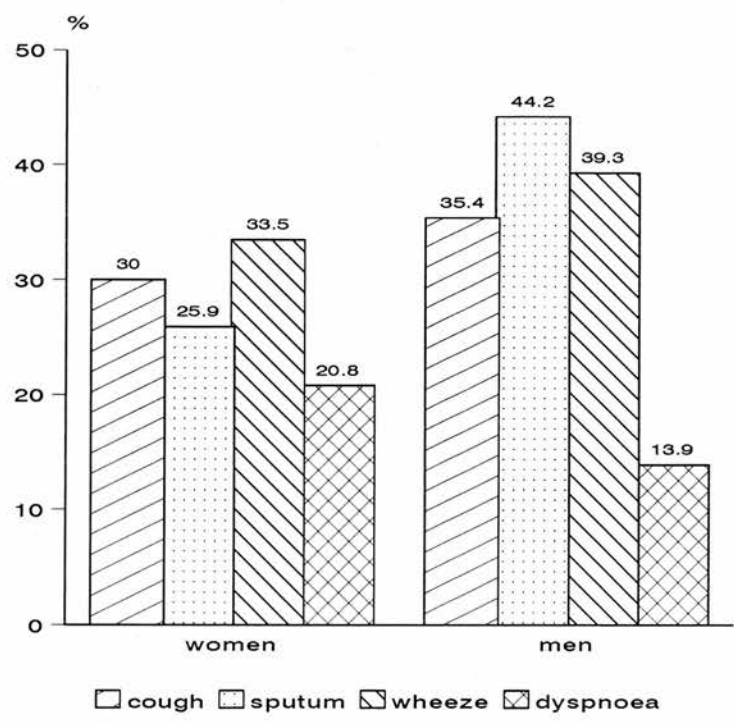
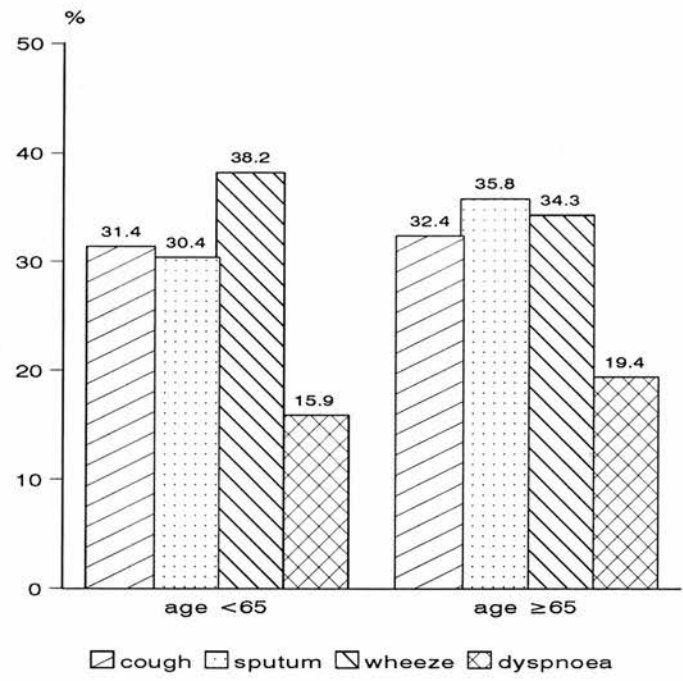


Figure 7.2: Respiratory symptoms reported by different age groups



difference in symptom prevalence between those aged <65 and ≥ 65 years.

Figure 7.3 shows symptoms reported by current, ex- and never-smokers. Both wheeze and sputum were more common in ex- than never-smokers (wheeze: $\chi^2=3.7$, $p=0.05$; sputum: $\chi^2=9.0$, $p=0.003$). Wheeze, cough and sputum were all more common in current than ex-smokers (wheeze: $\chi^2=8.2$, $p=0.004$; cough: $\chi^2=17.4$, $p=0.001$; sputum: $\chi^2=8.0$, $p=0.005$). Breathlessness was unrelated to smoking habit. In attenders, symptoms of chronic bronchitis were strongly associated with smoking habit (reported by 6/78 [7.7%] never-smokers, 15/93 [16.1%] ex-smokers and 30/73 [41.1%] current smokers [$\chi^2=27.5$, $p<0.001$]). In contrast, symptoms of bronchial irritability showed no relationship with smoking.

The 26 cigar or tobacco-smoking men reported relatively high levels of symptoms: 50.0% described cough, 65.4% sputum, 38.5% wheeze and 23.1% breathlessness.

Number of symptoms reported was also associated with smoking habit. Four symptoms were reported by 12% of current, 7.0% of ex- and only 2.4% of never-smokers; 30.4% of current, 47.9% of ex- and 57.2% of never-smokers were asymptomatic ($\chi^2=34.5$, $p<0.001$).

The relationship between symptoms and smoking habit changed with age. The proportion of never-smokers reporting one or more symptoms was 37.7% in younger adults (age <65 years), and 46.4% in older adults (age ≥ 65) ($p=0.26$); similar numbers of ex-smokers in the 2 age-groups were symptomatic, but symptoms were more common in younger than older current smokers (age <65 : 79.4% current smokers symptomatic, age ≥ 65 : 59.7% current smokers symptomatic; $\chi^2=6.2$, $p=0.01$).

Figure 7.4 shows symptoms in subjects reporting asthma or bronchitis. All symptoms were more common in those reporting a diagnosis. Subjects reporting

Figure 7.3: Respiratory symptoms reported by current, ex- and never-smokers

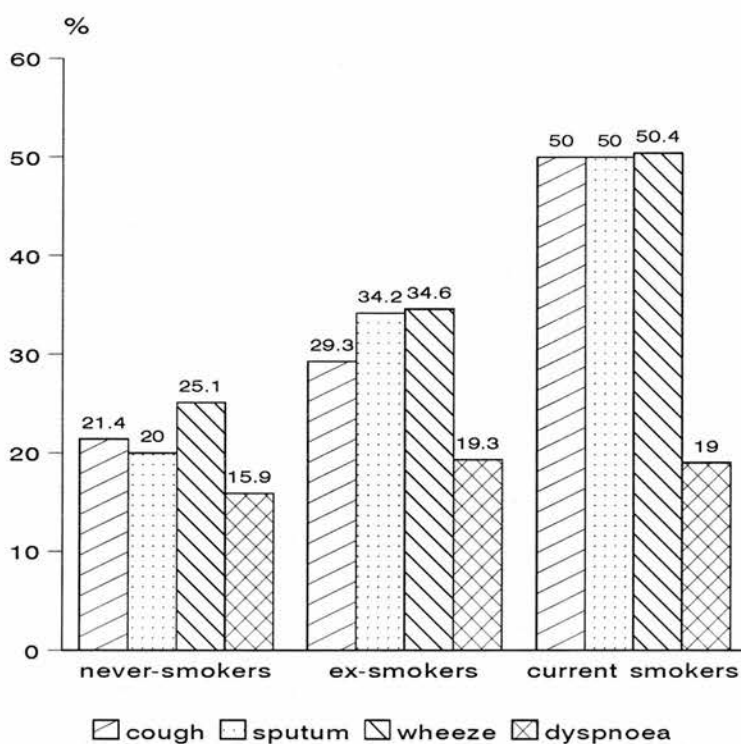
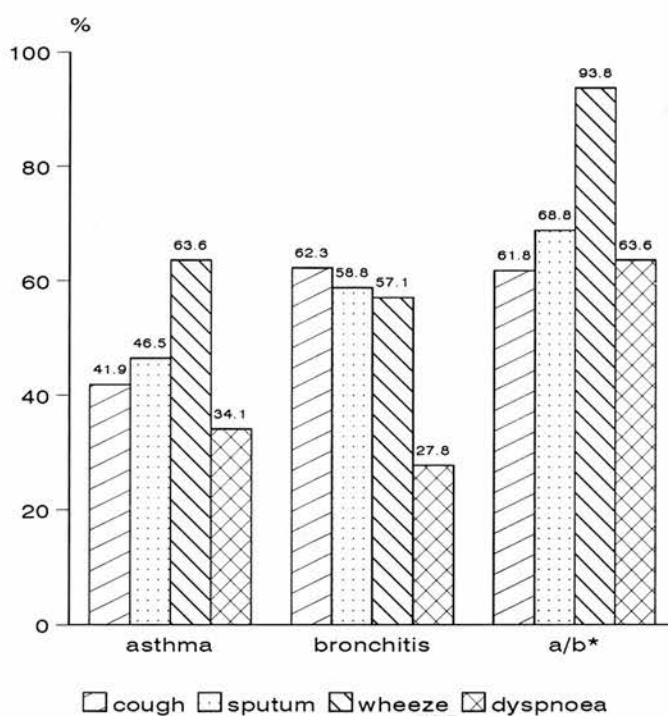


Figure 7.4: Respiratory symptoms in subjects reporting asthma, bronchitis, and asthma/bronchitis



* asthma/bronchitis

asthma alone described less cough than those reporting bronchitis ($\chi^2=5.1$, $p=0.02$), and less wheeze and breathlessness than subjects reporting asthma/bronchitis (wheeze: $\chi^2=9.3$, $p<0.002$, breathlessness: $\chi^2=6.6$, $p=0.01$). Although cough was less frequent in subjects with asthma than those with asthma/bronchitis, this difference did not reach significance ($\chi^2=3.0$, $p=0.08$). Subjects reporting bronchitis alone reported more cough than those reporting asthma (as above), and less wheeze and breathlessness than those reporting asthma/bronchitis (wheeze: $\chi^2=13.7$, $p<0.001$, breathlessness: $\chi^2=12.2$, $p<0.001$).

Symptoms of chronic bronchitis were reported by 24/167 (14.4%) attenders not reporting a diagnosis, 2/21 (9.5%) reporting asthma, 16/41 (39.0%) reporting bronchitis, and 9/17 (52.9%) of those reporting asthma/bronchitis ($\chi^2=24.8$, $p<0.001$). Of the bronchial irritability symptoms, wheeze/breathlessness on exposure to irritants was more common in subjects reporting a diagnosis (diagnosis: 68.4%, no diagnosis: 29.9%; $\chi^2=32.7$, $p<0.001$), as was morning wheeze (diagnosis: 30.4%, no diagnosis: 11.4%; $\chi^2=23.4$, $p<0.001$); nocturnal breathlessness was not related to the presence of a diagnosis.

Chapter 8: RESULTS OF SPIROMETRY

Reproducible spirometry results were available for 246 of the 247 attenders. Distribution of FEV₁ readings is shown in figure 8.1. For examination of the relationship between lung function and age, spirometry results were standardised to the mean height for women (1.58m) and men (1.71m), using the equation $FEV_1^* = FEV_1 / \text{height}^2 \times (\text{mean height})^2$, where FEV₁^{*} represents FEV₁ standardised to mean height (Burr et al. 1985). There was significant negative linear correlation between FEV₁^{*} and age in both sexes (women: $r = -0.60$, $p < 0.001$; men: $r = -0.47$, $p < 0.001$) (figure 8.2). FVC^{*} was also correlated with age (women: $r = -0.62$, $p < 0.001$; men: $r = -0.43$, $p < 0.001$) (figure 8.3). The relationship between FEV₁^{*}/FVC^{*} ratio and age was weaker, but still statistically significant (women: $r = -0.19$, $p = 0.01$; men: $r = -0.21$, $p = 0.01$) (figure 8.4). Unlike FEV₁^{*} and FVC^{*}, FEV₁^{*}/FVC^{*} ratio was not lower in women than men.

The effects of smoking on lung function are summarised in figures 8.5-8.7. In women, FEV₁^{*} was consistently lower in current and ex-smoking women than in never-smokers ($t = 2.6$, $p = 0.01$) (figure 8.5). However, the effect of smoking on FEV₁^{*} was less clear in men, with no difference between FEV₁^{*} in smoking and never-smoking men ($t = 1.0$, $p = 0.3$). Neither men or women showed a significant difference in FVC^{*} between smokers and never-smokers (women: $t = 1.1$, $p = 0.3$; men: $t = 1.0$, $p = 0.3$) (figure 8.6). Comparison of FEV₁^{*}/FVC^{*} ratio in smokers and never-smokers showed that in women, never-smokers had a higher ratio at all ages ($t = 4.2$, $p < 0.0001$), whereas in men ratios were similar in smokers and never-smokers ($t = 0.6$, $p = 0.6$) (figure 8.7).

In order to compare lung function in the Central Manchester population with that measured in other cross-sectional population studies, measured FEV₁ was compared with values predicted by equations derived from 5 such studies (Cotes et al. 1966; Burr et al. 1985; Dockery et al. 1985; Roberts et al. 1991; Enright et al. 1993). The populations from which these prediction equations were derived are compared in table 8.1; since most included only healthy never-smokers, current and ex-smokers were excluded from the Central Manchester population.

Figure 8.1: Distribution of FEV₁

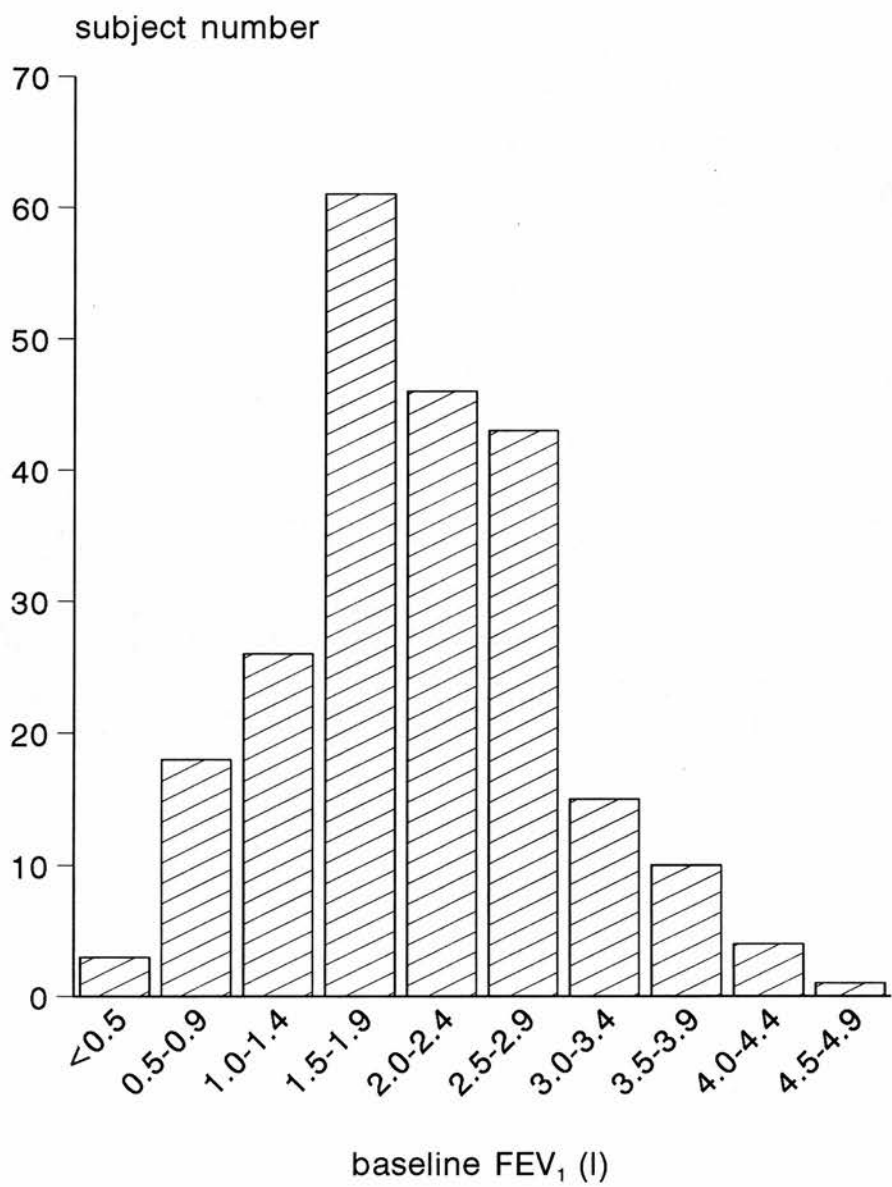
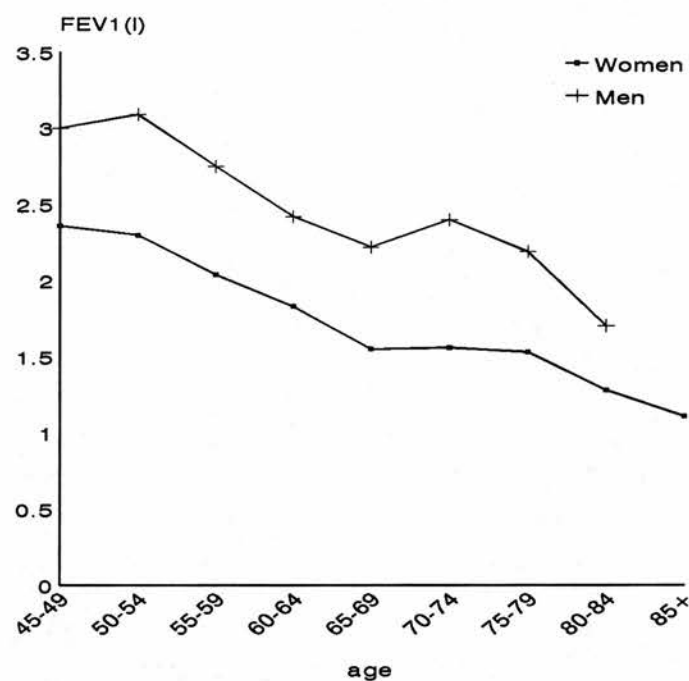
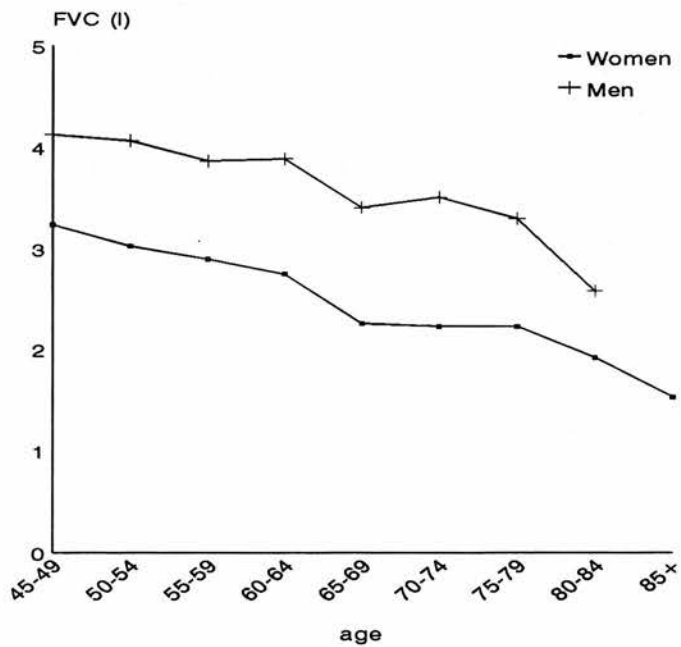


Figure 8.2: FEV1 vs age for Central Manchester adults



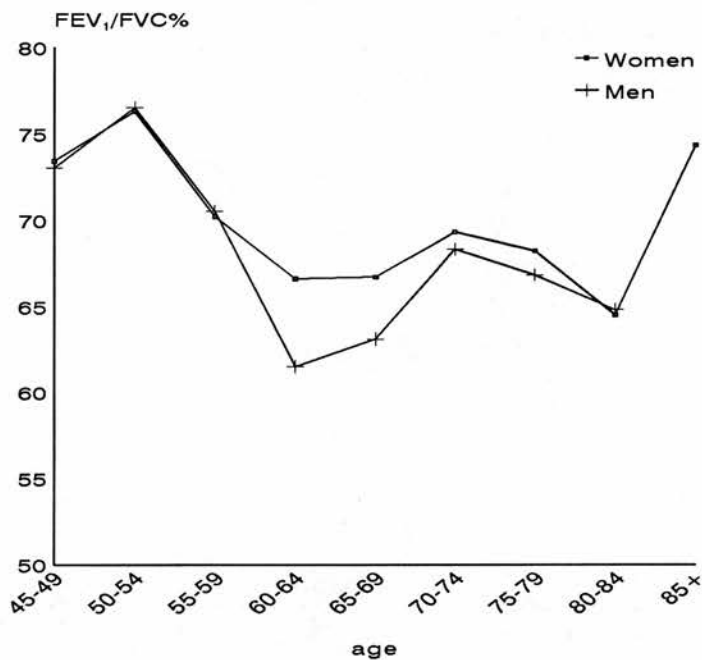
FEV1 standardised to mean height

Figure 8.3: FVC vs age for Central Manchester adults



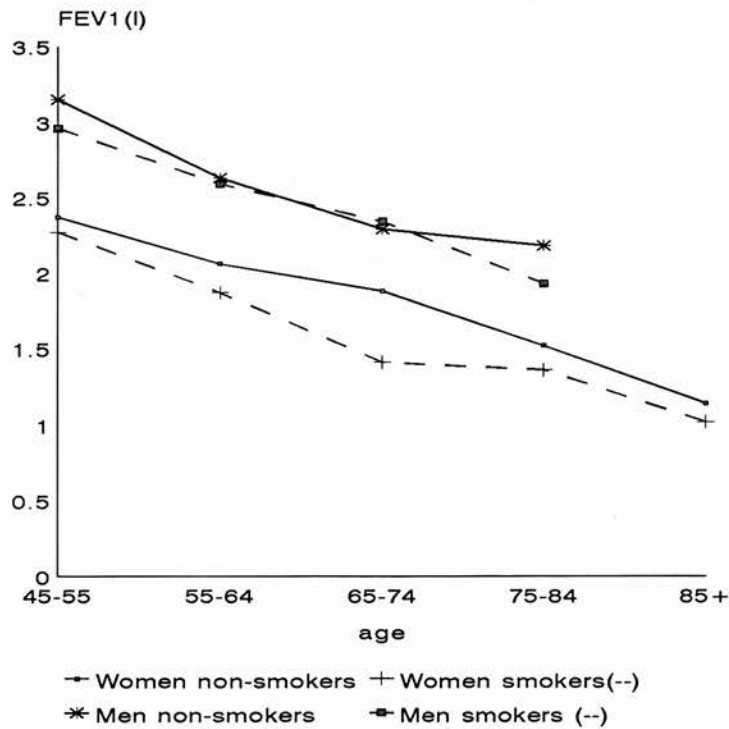
FVC standardised to mean height

Figure 8.4: FEV₁/FVC vs age for Central Manchester adults



FEV₁ and FVC standardised to mean age

Figure 8.5: FEV₁ in smokers and never-smokers



FEV₁ adjusted to mean height

Figure 8.6: FVC in smokers and never-smokers

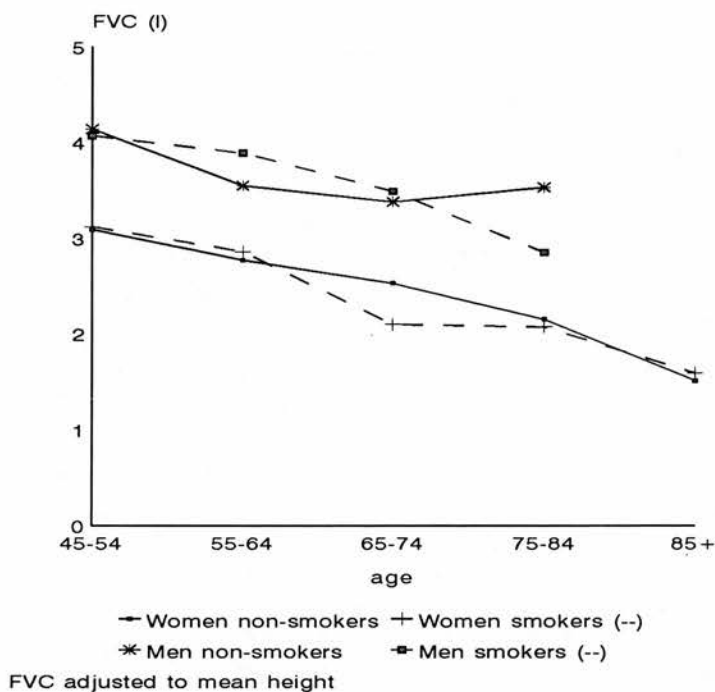


Figure 8.7: FEV₁/FVC% in smokers and never-smokers

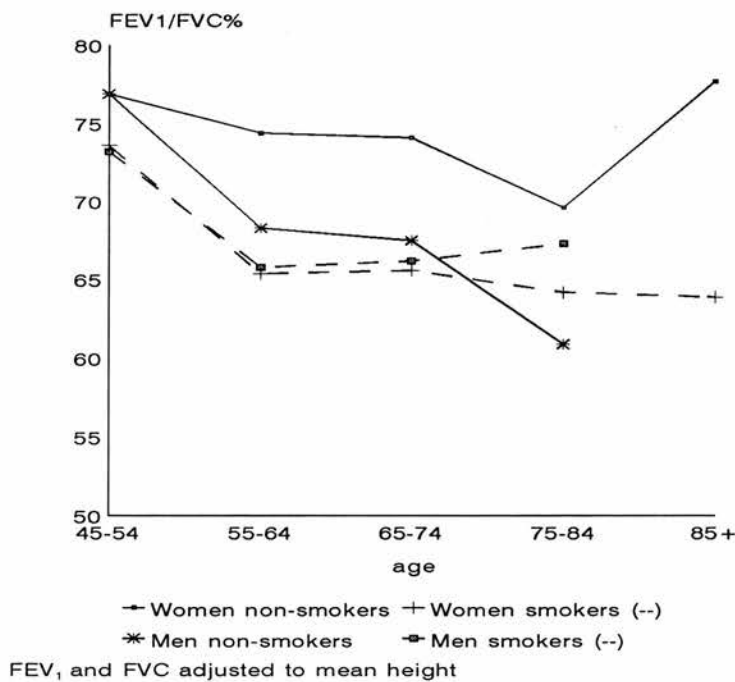


Table 8.1: Features of published reference ranges

Authors	Sample	n	Age range	Exclusions
Cotes et al, 1966	Random sample working men	275	20-64	Dusty occupations Lung disease Breathlessness
Burr et al, 1985	Random sample	418	70+	Residents of institutions#
Dockery et al, 1985	Random sample	2454*	25-74	Smokers Symptoms
Roberts et al, 1991	Volunteers	179	18-86	Smokers Symptoms Lung disease
Enright et al, 1993	Random sample	777**	65-85	Smokers Lung disease Symptoms Others##

*30% of screened population; **15% of screened population

#smokers included but analysed separately; ##hypertension, diabetes, heart disease, obesity etc

For women, measured FEV_1 in never-smokers was similar to values predicted by Cotes ($t=1.1$, $p=0.3$), Burr ($t=1.0$, $p=0.3$) and Dockery ($t=-0.6$, $p=0.5$). However, measured FEV_1 in women was lower than values predicted by Enright et al ($t=-2.6$, $p=0.02$), and Roberts et al ($t=-4.7$, $p<0.0001$) (figure 8.8). In contrast, measured FEV_1 for never-smoking men was lower than all 5 sets of predicted values, with this difference being statistically significant for values predicted by Dockery et al ($t=-4.4$, $p=0.0006$), Enright et al ($t=-2.3$, $p=0.05$) and Roberts et al ($t=-4.8$, $p=0.0001$), but not for those predicted by Cotes ($t=-1.8$, $p=0.09$) and Burr ($t=-2.2$, $p=0.06$) (figure 8.9). Removal of subjects with respiratory symptoms from the comparison did not affect these results: in asymptomatic never-smoking women, FEV_1 predicted by Enright ($t=-4.5$, $p=0.0001$) and Roberts ($t=-4.3$, $p=0.0002$) was higher than measured FEV_1 , and the same was true for values predicted by Dockery ($t=-3.1$, $p=0.01$), Enright ($t=-2.0$, $p=0.06$) and Roberts ($t=-3.0$, $p=0.01$) in asymptomatic never-smoking men.

Figure 8.8: Actual FEV₁ vs predicted using equations of Cotes, Enright, Dockery, Roberts and Burr - never-smoking women

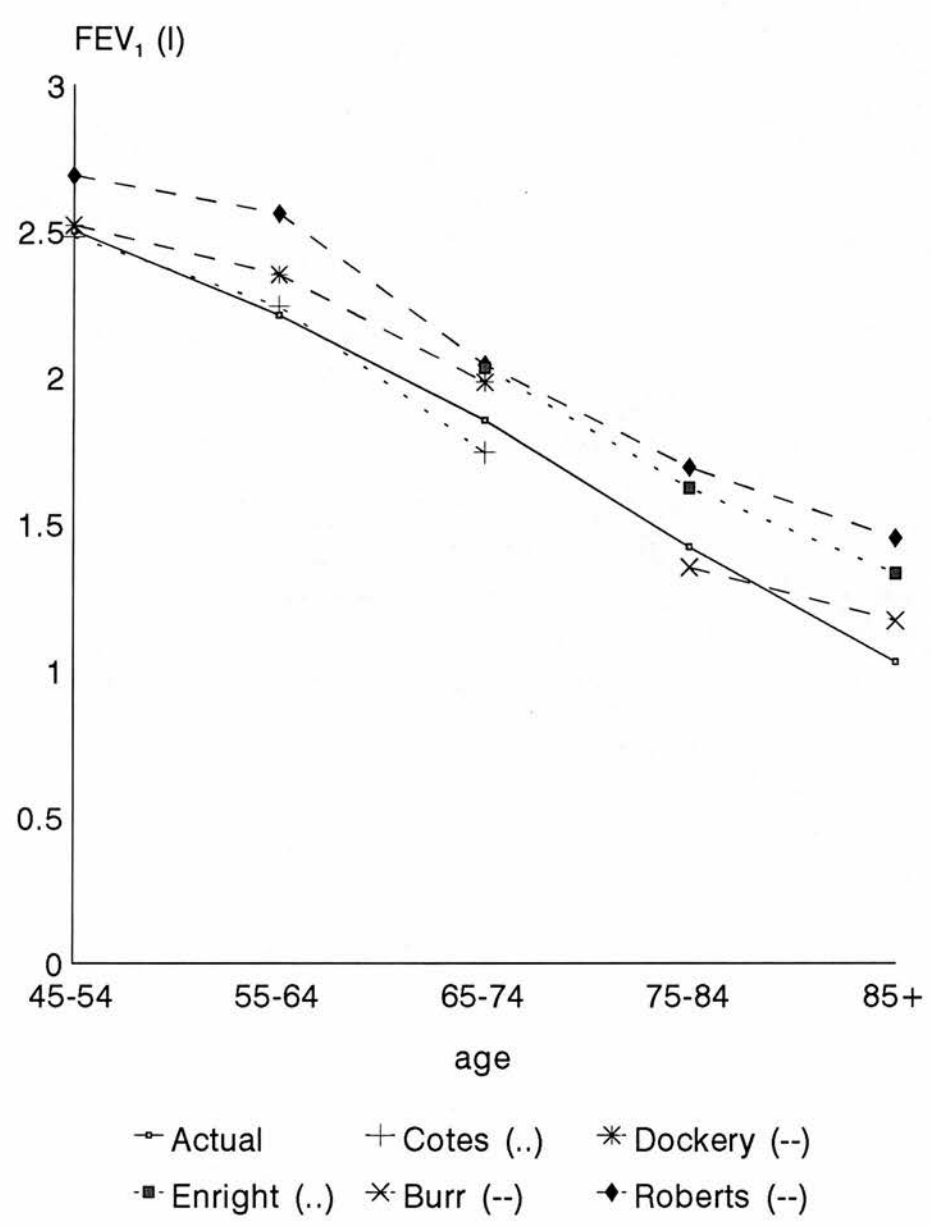
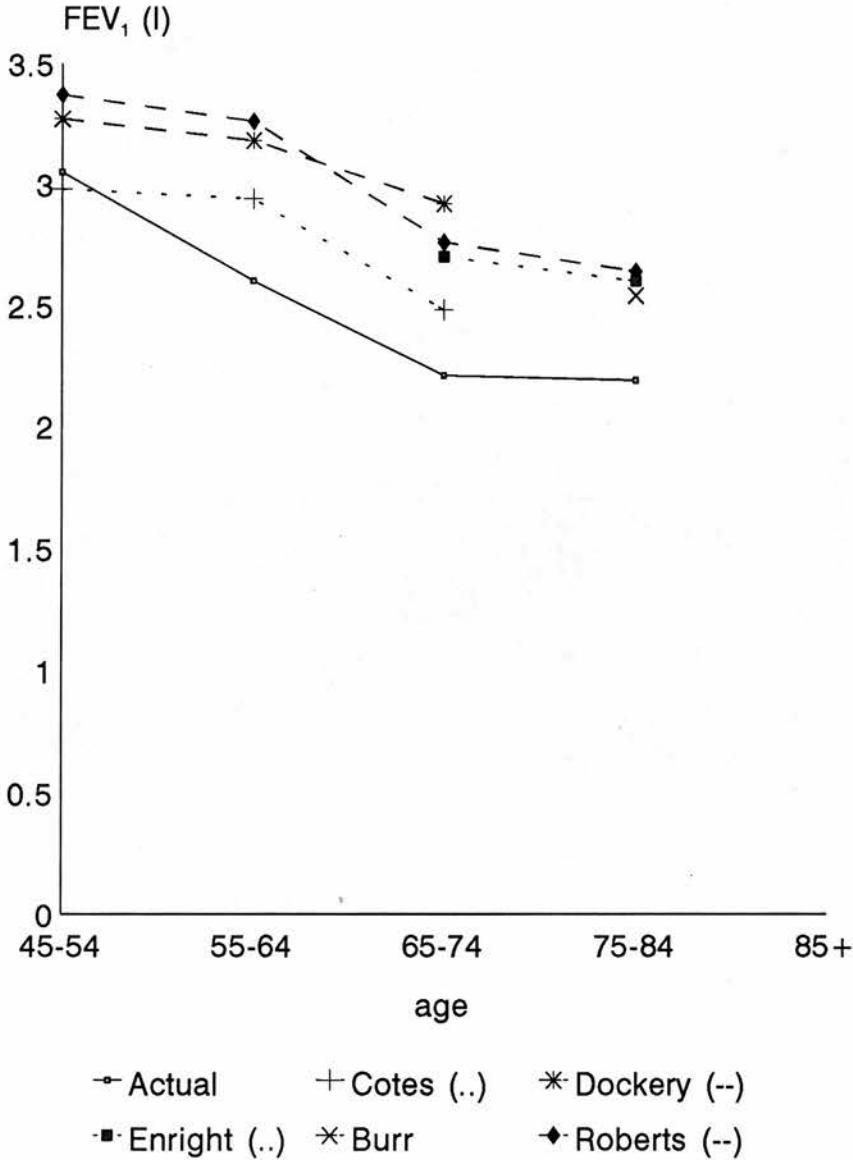


Figure 8.9: Actual FEV₁ vs predicted, using equations of Cotes, Enright, Dockery and Burr - never-smoking men



**Chapter 9: PREVALENCE OF CHRONIC AIRFLOW OBSTRUCTION AND
REVERSIBILITY**

(Renwick and Connolly, 1996a)

Ratio of FEV_1/FVC is frequently used as a measure of airflow obstruction, with a ratio of 70-80% being regarded as normal. For the purposes of this study, chronic airflow obstruction was defined as $FEV_1/FVC\% < 65\%$; this gave a prevalence of 29.3% (72/246 subjects performing spirometry). However, as $FEV_1/FVC\%$ decreases with age in this population (see Chapter 8), there was a risk that use of this definition would lead to over-estimation of airflow obstruction in older subjects. To prevent this, in subjects aged ≥ 65 a predicted value and lower limit of normal (fifth percentile) for $FEV_1/FVC\%$ were calculated using reference ranges derived from the Cardiovascular Health Study (a recent cross-sectional survey of adults aged ≥ 65 years) (Enright et al. 1993). Chronic airflow obstruction was then defined as $FEV_1/FVC\% < 65\%$ for subjects aged < 65 , and as $FEV_1/FVC\%$ below lower limit of predicted value for subjects aged ≥ 65 . Using this composite definition, 65 subjects (26.4%) had chronic airflow obstruction.

Chronic airflow obstruction was equally prevalent in women and men ($\chi^2=0.25$, $p=0.6$) (Figure 9.1), and in older and younger adults ($\chi^2=1.46$, $p=0.2$) (Figure 9.2). There was a strong relationship with smoking, with chronic airflow obstruction being more in common ex- than never-smokers ($\chi^2=5.7$, $p=0.02$). However, the difference between ex- and current smokers did not reach significance (Figure 9.3). Only 15.4% of subjects with airflow obstruction had never smoked, compared with 37.8% of those without airflow obstruction ($\chi^2=11.0$, $p=0.001$).

Subjects with chronic airflow obstruction were more likely to report asthma and/or bronchitis than those with no airflow obstruction (airflow obstruction: 55.4% asthma and/or bronchitis, no airflow obstruction: 23.8% asthma and/or bronchitis; $\chi^2=26.1$, $p<0.001$). The prevalence of chronic airflow obstruction was similar in those reporting asthma alone and bronchitis alone. Although airflow obstruction appeared to be more common in those with asthma/bronchitis than in those reporting a single diagnosis, this difference was not statistically significant (Figure 9.4).

The validity of a questionnaire report of asthma/bronchitis for identification of

Figure 9.1: Prevalence of chronic airflow obstruction in women and men

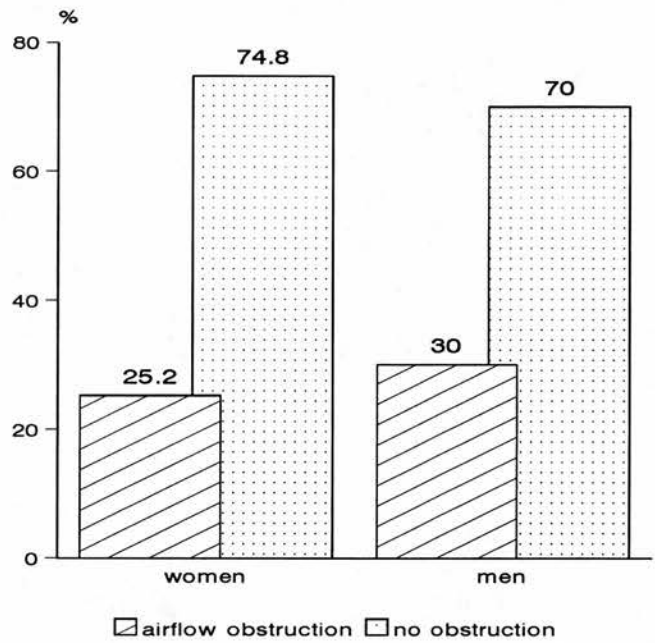


Figure 9.2: Prevalence of chronic airflow obstruction in older and younger adults

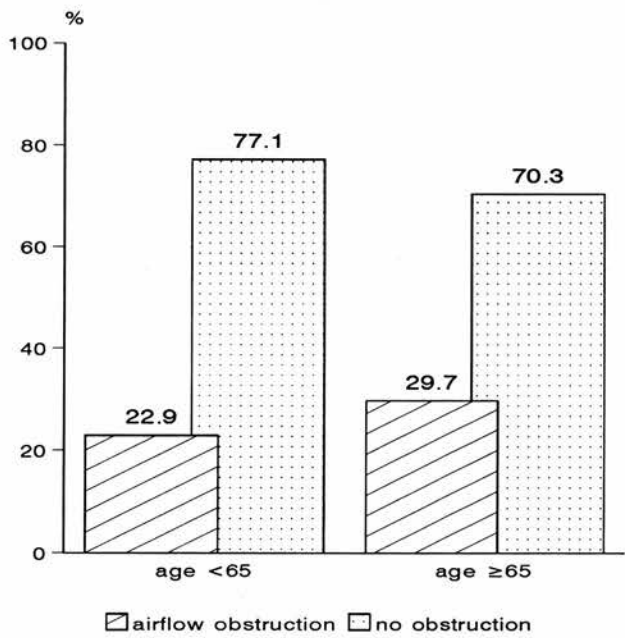


Figure 9.3: Prevalence of chronic airflow obstruction in smokers and non-smokers

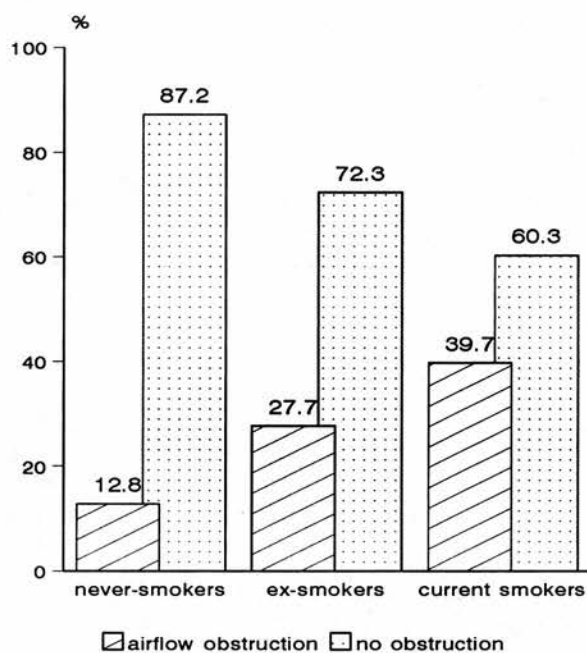
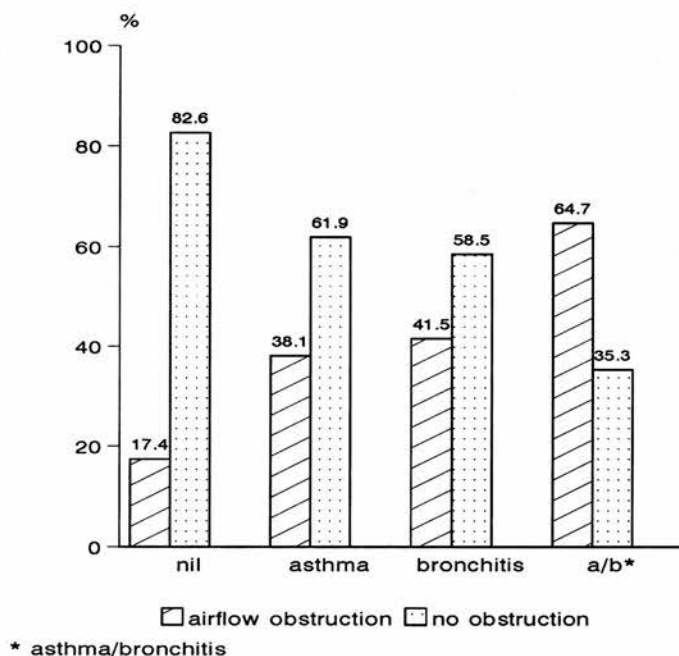


Figure 9.4: Prevalence of chronic airflow obstruction in subjects reporting asthma and bronchitis

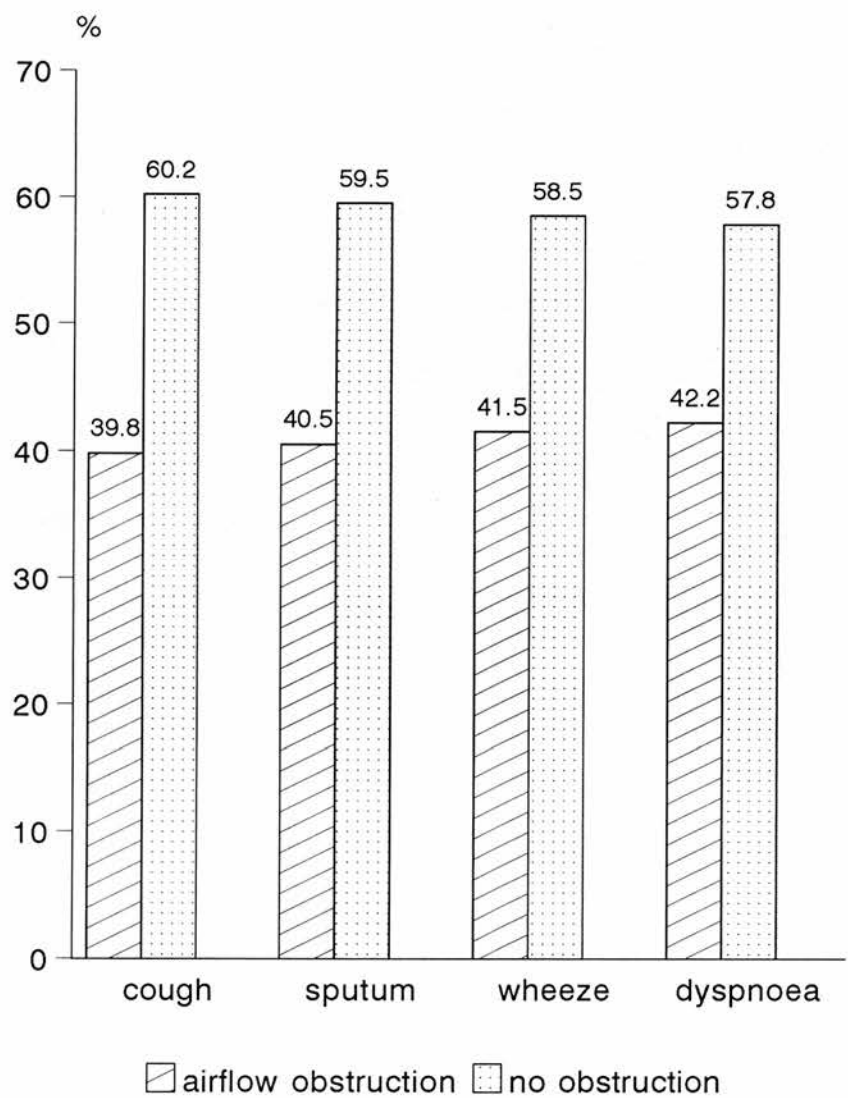


subjects with chronic airflow obstruction can be assessed by calculation of the positive predictive value (the proportion of those reporting a diagnosis who have proven airflow obstruction), sensitivity (the proportion of those with airflow obstruction who report a diagnosis), and specificity (the proportion of those who do not have airflow obstruction who do not report a diagnosis). The positive predictive value of a reported diagnosis (asthma and/or bronchitis) for airflow obstruction was 45.6% (sensitivity 55.3%, specificity 76.2%); 48.1% of subjects reporting bronchitis had chronic airflow obstruction (sensitivity 43.3%, specificity 80.3%).

Respiratory symptoms were reported more frequently by subjects with chronic airflow obstruction: 50 (76.6%) of those with chronic airflow obstruction were symptomatic, compared with 50.0% of those without airflow obstruction ($\chi^2=13.5$, $p<0.001$). However, less than half of subjects reporting cough or sputum had airflow obstruction (figure 9.5). Subjects with chronic airflow obstruction were more likely to report multiple symptoms: 18.8% of those with airflow obstruction and 3.4% of those without reported 4 symptoms ($\chi^2=25.8$, $p<0.001$). However, because symptoms were common in those with no airflow obstruction, the positive predictive value of one or more symptoms for chronic airflow obstruction was only 35.8% (sensitivity 76.6%, specificity 50.0%). The positive predictive value of having 4 symptoms was 66.7% (sensitivity 18.8%, specificity 96.6%).

Symptoms of chronic bronchitis were more common in attenders with airflow obstruction (24/65 [36.9%] vs 27/181 [15.0%]; $\chi^2=13.9$, $p<0.001$), as were symptoms of bronchial irritability (breathlessness/wheeze on exposure to irritants: 63.1% vs 35.0% [$\chi^2=15.4$, $p<0.001$]; morning wheeze: 29% vs 13% [$\chi^2=8.3$, $p=0.004$]; nocturnal breathlessness: 13.9% vs 5.0% [$\chi^2=5.5$, $p=0.02$]). Symptoms of chronic bronchitis (chronic productive cough) were related more strongly to chronic airflow obstruction than were other symptoms (positive predictive value 47.1%, sensitivity 36.9%, specificity 85.0%).

Figure 9.5: Prevalence of chronic airflow obstruction in subjects with respiratory symptoms



Separate analysis of older and younger subjects revealed no difference in the relationship between chronic airflow obstruction and respiratory symptoms; predictive values of symptoms and reported diagnoses were similar in both age groups.

Reversibility of airflow obstruction was assessed in 22 subjects with baseline FEV_1 too low for bronchial challenge (ie $< 60\%$ predicted). Ten of these subjects (45.5%) had ≥ 160 ml improvement in FEV_1 following terbutaline inhalation. There was no significant difference in age or level of airflow obstruction between these subjects and those with no reversibility; numbers were too small to allow comparison of reversibility in those reporting asthma and/or bronchitis, or in smokers and never-smokers. However, there did appear to be a sex difference: 2/11 women (18%) and 8/11 men (73%) had reversible airflow obstruction ($\chi^2=6.6$, $p=0.01$).

Chapter 10: PREVALENCE OF INCREASED BRONCHIAL
RESPONSIVENESS

Of the 208 subjects completing methacholine challenge, 148 (71.1%) achieved a PD_{20} (ie had $\geq 20\%$ fall in FEV_1 from baseline). Distribution of PD_{20} measurements in the population is shown in figure 10.1. Bronchial responsiveness was slightly increased (PD_{20} 100-800 μ g) in 52 subjects (25.0%), moderately increased (PD_{20} 12.5-100 μ g) in 42 (20.2%), and greatly increased ($PD_{20} \leq 12.5\mu$ g) in 12 subjects (5.8%).

Figure 10.2 shows levels of bronchial responsiveness in men and women; there was no significant difference between the sexes. The prevalence of increased bronchial responsiveness was similar in those aged < 65 and ≥ 65 years ($\chi^2=3.0$, $p=0.4$) (figure 10.3).

The prevalence of slightly and moderately increased bronchial responsiveness was higher in current smokers than never-smokers ($\chi^2=7.8$, $p=0.02$) (Figure 10.4). Ex-smokers had a similar prevalence of increased bronchial responsiveness to never-smokers. $PD_{20} \leq 12.5\mu$ g was not associated with smoking habit.

The prevalence of increased bronchial responsiveness in subjects reporting bronchitis alone was similar to those reporting no diagnosis (Figure 10.5). Subjects reporting asthma alone had similar levels of increased bronchial responsiveness to those reporting asthma/bronchitis. Both moderately and greatly increased bronchial responsiveness were found more frequently in subjects reporting asthma or asthma/bronchitis than those reporting bronchitis or no diagnosis ($PD_{20} \leq 100\mu$ g: $\chi^2=41.9$, $p<0.001$; $PD_{20} \leq 12.5\mu$ g: $\chi^2=34.1$, $p<0.001$). Of subjects reporting either asthma or asthma/bronchitis, 96.3% had at least slightly increased bronchial responsiveness, and 77.8% had moderately or greatly increased bronchial responsiveness. The positive predictive value of reported asthma for $PD_{20} \leq 100\mu$ g was 77.8% (sensitivity 38.9%, specificity 96.1%).

All levels of bronchial hyper-responsiveness were more common in symptomatic than asymptomatic subjects: $PD_{20} \leq 100\mu$ g was found in 36.8% of symptomatic and

Figure 10.1: Distribution of PD₂₀

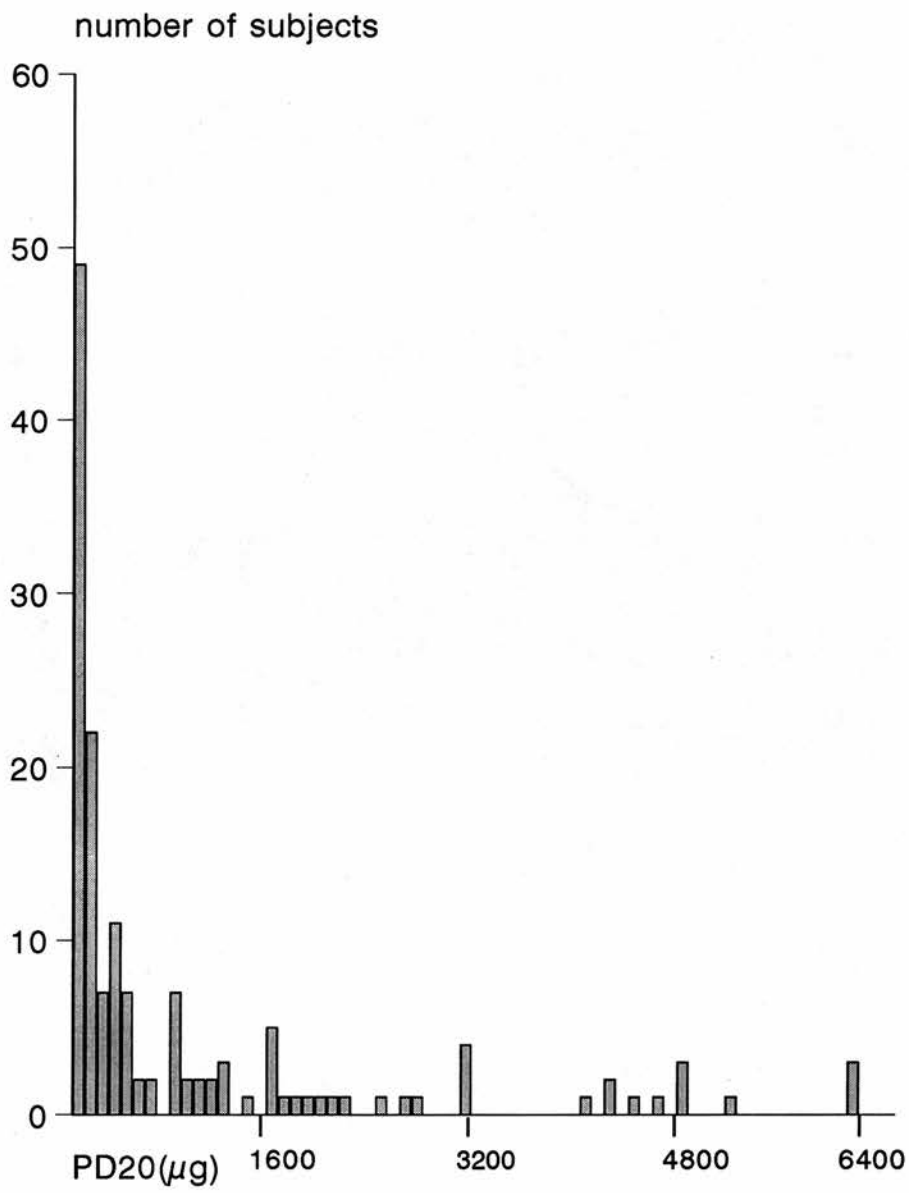


Figure 10.2: Prevalence of increased bronchial responsiveness in men and women

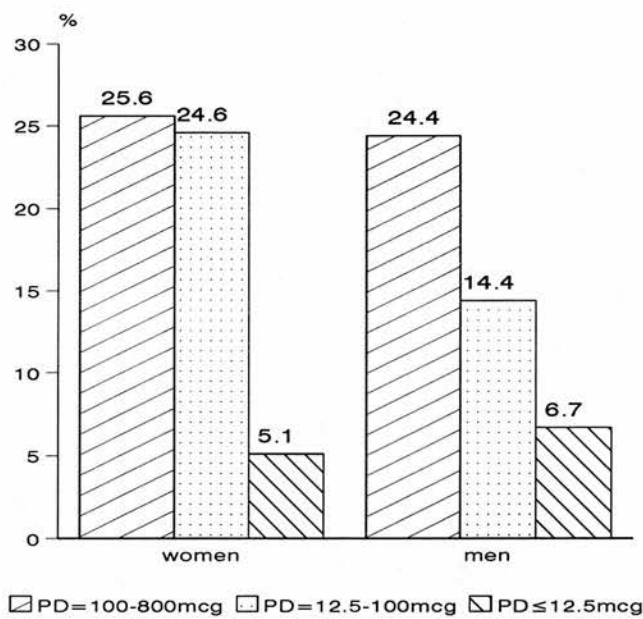


Figure 10.3: Prevalence of increased bronchial responsiveness in older and younger adults

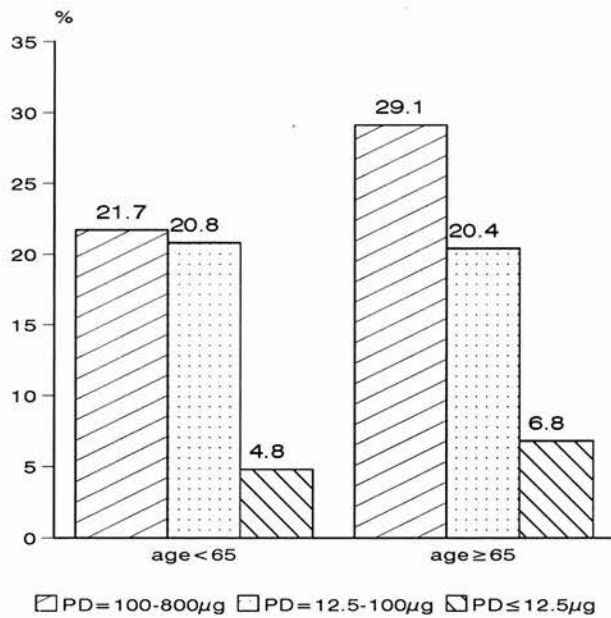


Figure 10.4: Prevalence of increased bronchial responsiveness in smokers and non-smokers

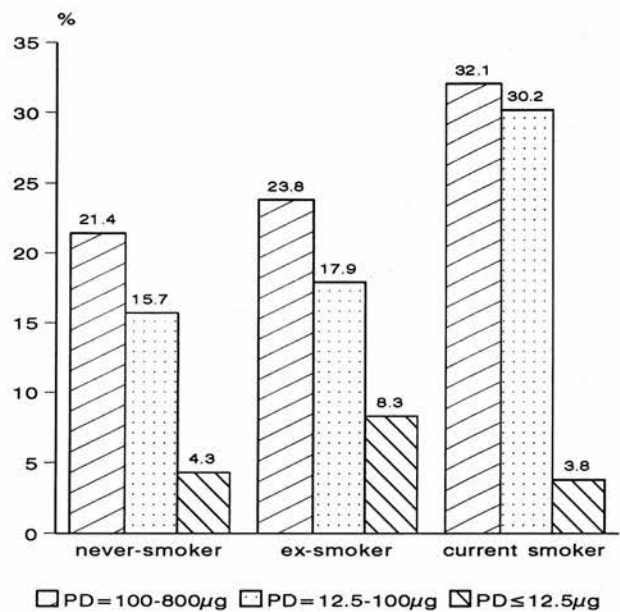
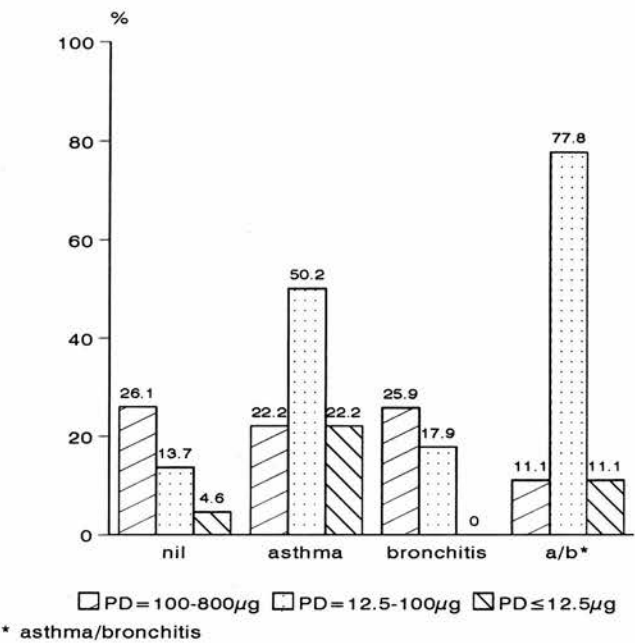


Figure 10.5: Prevalence of increased bronchial responsiveness in subjects reporting asthma and bronchitis



14.6% of asymptomatic subjects ($\chi^2=25.0$, $p<0.001$). In all, 26.4% of those with $PD_{20}\leq 100\mu g$ were asymptomatic. Asymptomatic bronchial hyper-responsiveness was slightly more common in older subjects (age ≥ 65 : 19/54 [35.2%] subjects with $PD\leq 800\mu g$ were asymptomatic vs 12/48 [25.0%] age <65), but this difference failed to reach significance ($\chi^2=1.2$, $p=0.3$). Subjects with higher numbers of symptoms were more likely to have increased bronchial responsiveness: $PD_{20}\leq 100\mu g$ was found in 14.6% of asymptomatic subjects, and 83.3% of those with 4 symptoms ($\chi^2=20.1$, $p<0.001$).

Figure 10.6 shows bronchial responsiveness in subjects reporting different respiratory symptoms. Whilst cough and sputum were reported commonly by subjects with slightly increased bronchial responsiveness, moderately and greatly increased bronchial responsiveness were particularly associated with the presence of wheeze or breathlessness. The positive predictive value of reported wheeze for $PD_{20}\leq 100\mu g$ was 49.3% (sensitivity 64.2%, specificity 77.0%); breathlessness had a positive predictive value for $PD_{20}\leq 100\mu g$ of 50.0% (sensitivity 26.4%, specificity 90.9%). Symptoms of "bronchial irritability" were also more common in subjects with bronchial hyper-responsiveness, but did not show a stronger association than that of breathlessness or wheeze. The presence of one or more bronchial irritability symptoms had a positive predictive value of 34.9% for $PD_{20}\leq 100\mu g$ (sensitivity 55.6%, specificity 63.6%).

Bronchial hyper-responsiveness ($PD_{20}\leq 100\mu g$) plus wheeze or breathlessness was present in 15.0% of the Central Manchester population, and was equally common in women and men, and in subjects aged <65 and ≥ 65 years. This has been suggested by some authors as a definition of asthma for use in epidemiological surveys, as it removes the problem of how to interpret asymptomatic bronchial hyper-responsiveness (Toelle et al. 1992). The positive predictive value of reported asthma or asthma/bronchitis for asthma defined in this way was 47.4% (sensitivity 48.6%, specificity 90.4%).

Figure 10.6: Prevalence of increased bronchial responsiveness in subjects with respiratory symptoms

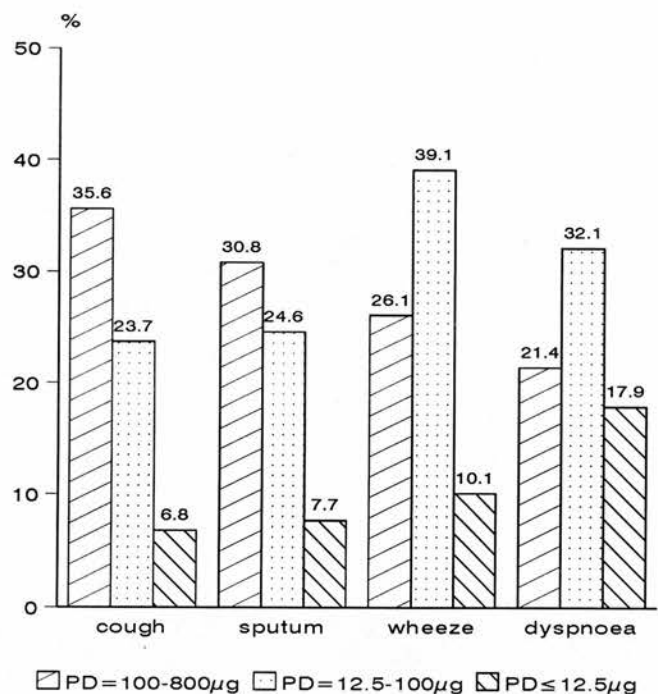
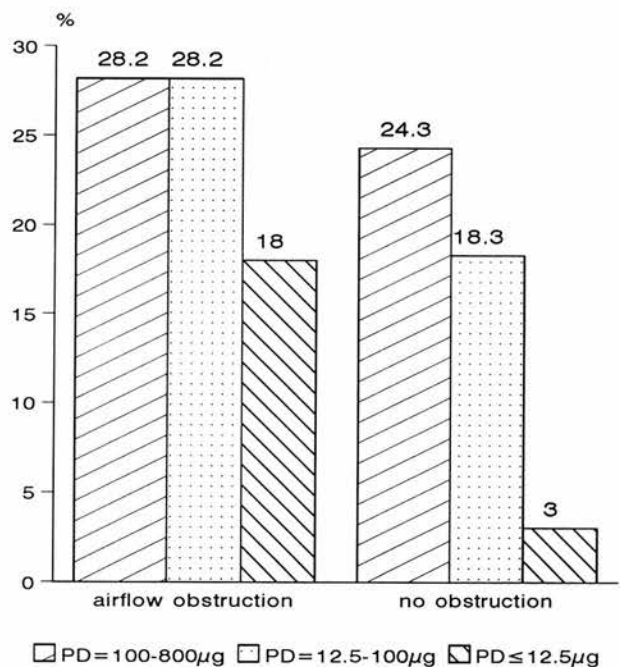


Figure 10.7: Prevalence of increased bronchial responsiveness in subjects with chronic airflow obstruction



Increased bronchial responsiveness was more common in subjects with chronic airflow obstruction ($\chi^2=19.4$, $p<0.001$) (Figure 10.7). There was a dose-response relationship between degree of airflow obstruction and level of bronchial responsiveness, with positive linear correlation between PD_{20} (log transformed to achieve normal distribution) and FEV_1/FVC ratio ($n=148$; $r=0.35$, $p<0.0001$), and negative linear correlation between log dose-response slope and FEV_1/FVC ratio ($n=208$; $r=-0.4$, $p<0.0001$).

**Chapter 11: RELATIONSHIP BETWEEN BRONCHIAL RESPONSIVENESS
AND AGE: ANALYSIS BY MULTIPLE REGRESSION**

Analysis of the relationship between age and bronchial responsiveness with the latter expressed as a categorical variable (increased vs not increased) fails to take into account the effects of other variables associated with both age and bronchial responsiveness (eg baseline FEV₁, smoking habit). Furthermore, analysis using a continuous measure allows the use of statistical tests which have increased power for detecting inter-relationships between bronchial responsiveness and other variables. The published literature suggests that nonspecific bronchial responsiveness may be associated with age, sex, smoking habit, atopy, and baseline airways calibre. Multiple regression analysis was used to assess whether age had an independent relationship with bronchial responsiveness when the effects of these other variables were taken into consideration.

i) Statistical methods

For multiple regression analysis, bronchial responsiveness was expressed as dose-response slope, and values were log transformed to achieve normal distribution. One subject had a slight increase in FEV₁ during bronchial challenge, producing a negative dose-response slope; to allow logarithmic conversion of this result, a constant of 0.43 was added to all dose-response slope values (Sparrow et al. 1994).

Several of the independent variables in the regression equation (age, sex, smoking, airways calibre and atopy) showed inter-relationships. Where possible, these inter-relationships were removed by standardisation of variables for age and sex. Thus, as eosinophil counts and total IgE levels are dependent on age and sex (Burrows et al. 1980; Wittig et al. 1980; Barbee et al. 1981), they were converted to standardised "Z-scores" (Burrows and et al. 1989). The Z-score indicates the number of standard deviations by which each IgE level or eosinophil count differs from the mean value of the appropriate sex and age group (age 45-54, 55-64, 65-74, >75 years). To allow conversion to Z-scores, 46 subjects with IgE level reported as <5 IU/ml were given the value of 0.1 IU/ml. Z-scores were log transformed to achieve normal distribution.

Measures of airways calibre are also strongly related to age and sex, and so FEV_1 or FEV_1/FVC ratio are not suitable for use in regression analysis. Expression of FEV_1 as % predicted values does not entirely remove age and sex bias: as FEV_1 increases with height and decreases with age, the use of % predicted FEV_1 will lead to an increase in the number of elderly and short individuals appearing to have abnormal results (Miller and Pincock 1988). This is obviously relevant in the current study, which contains many elderly subjects. To avoid this bias, the use of standardised residuals (SR) has been recommended (Miller and Pincock 1988). These are calculated using the equation $SR = (\text{recorded value} - \text{predicted value})/RSD$, where RSD is the residual standard deviation about the regression equation used to calculate the predicted values (Miller et al. 1985). For the current study, standardised residuals were calculated using prediction equations derived from a study of urban white UK adults over a wide age range (Roberts et al. 1991). The distribution of standardised residuals is shown in figure 11.1.

Where inter-relationships between independent variables persisted (eg between airways calibre and smoking habit), interaction terms were included in the regression equation (Sparrow et al. 1994).

ii) Results

Table 11.1 summarises the results of stepwise multiple regression analysis with bronchial responsiveness (expressed as log dose-response slope) as the dependent variable, and age, sex, packyears smoked, airways calibre (expressed as FEV_1 standardised residuals), IgE (expressed as log Z-score) and eosinophils (log Z-score) as independent variables. Bronchial responsiveness was positively associated with IgE and with age; there was a negative relationship between bronchial responsiveness and airways calibre. Packyears smoked, sex, and eosinophils were not independently associated with bronchial responsiveness. The inclusion of interaction factors for the relationship between airways calibre and packyears smoked, and between sex and packyears smoked, did not alter either the value of R^2 or the relationships between other variables. The interaction factors themselves

Figure 11.1: Distribution of baseline FEV₁ (standardised residuals)

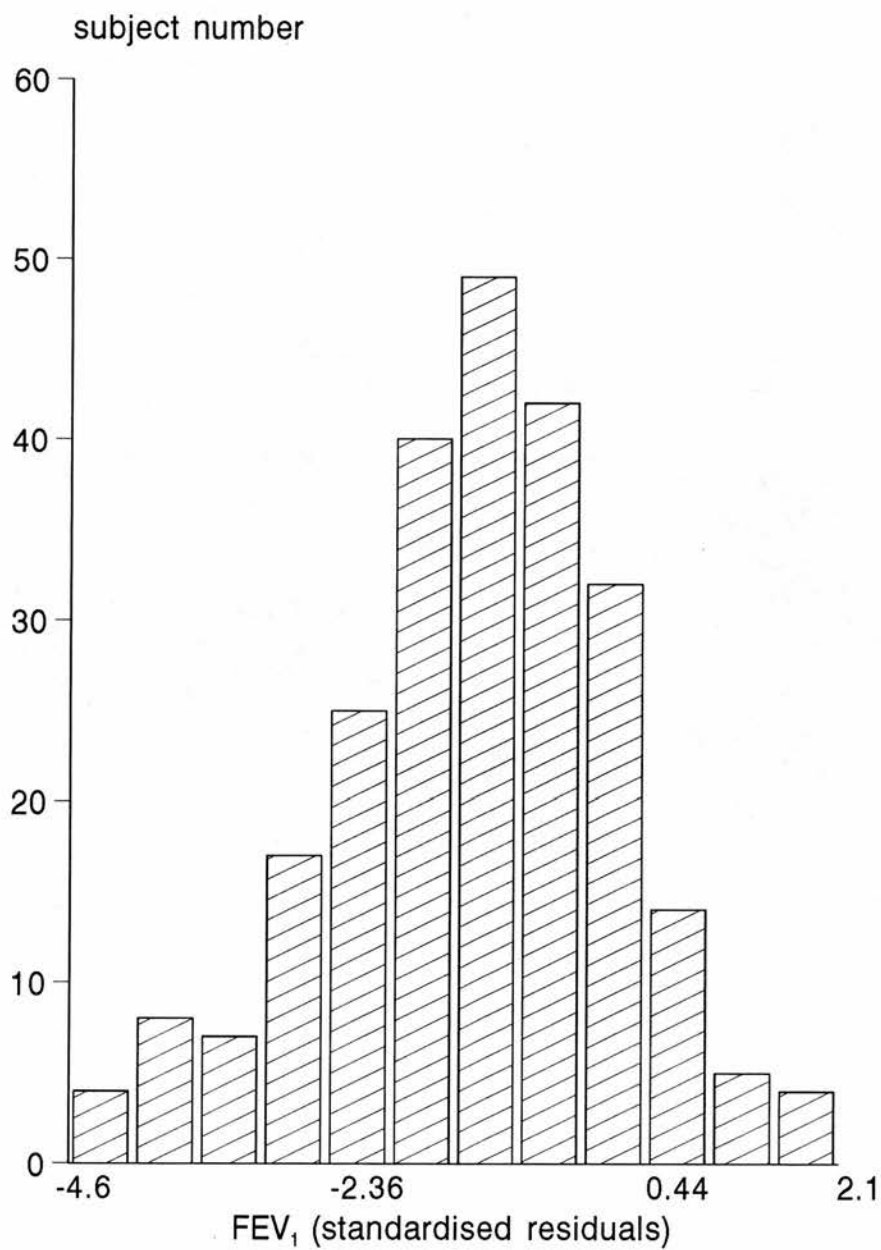


Table 11.1: Factors associated with bronchial responsiveness:
stepwise multiple regression analysis

Independent variable	B	SE	t	p	% var
FEV1*	-0.49	0.07	-7.42	<0.0001	21
IgE#	0.22	0.07	3.28	0.001	3
age	0.01	0.006	2.39	0.02	3
sex	-0.16	0.13	-1.23	0.22	
packyears	0.005	0.003	1.81	0.07	
eosinophils#	0.08	0.07	1.08	0.28	

$R^2=0.29$

* standardised residuals # log Z-score

%var=percent of variation in dependent variable attributable to independent variable

were not significantly associated with bronchial responsiveness.

Chapter 12: RELATIONSHIP BETWEEN BRONCHIAL RESPONSIVENESS
AND ATOPY

The strong relationship between atopy and asthma in children and young adults is undisputed, and measures of atopy have been shown to correlate with bronchial responsiveness in young populations (Cockcroft et al. 1984). However, it is generally assumed that the role of atopy is less important in adult-onset asthma (so-called "intrinsic" asthma). As far as chronic bronchitis is concerned, this has been regarded as a consequence of smoking rather than an atopic disease, although a relationship between measures of atopy and airways calibre in smokers with chronic airflow obstruction was predicted by the "Dutch Hypothesis" (see page 12). We have investigated the links between atopy, airways calibre and bronchial responsiveness in our random population sample.

i) Methods

Questions about personal or family history of atopy (hay fever, contact dermatitis or eczema) were included in the full questionnaire. A venous blood sample was taken from subjects attending for bronchial challenge, and was sent to the hospital laboratories for measurement of total IgE and eosinophil count. Skin tests were not performed due to lack of time and staff. Both IgE levels and eosinophil counts were converted to age- and sex-adjusted Z-scores as described on page 142; log values of Z scores were used to achieve normal distribution. Relationships between IgE/eosinophils and lung function were assessed by t test and multiple regression analysis.

ii) Results

Atopy was reported by 132 subjects (26.1%) completing the full questionnaire, and 163 (32.4%) reported atopy in a first degree relative. Of the 247 subjects attending for methacholine challenge, total IgE measurements were available for 235, and eosinophil counts for 231. Missing results represent refusal of blood testing, and problems with delivery or laboratory analysis of samples.

The distribution of total IgE level and eosinophil counts are shown in figures 12.1 and 12.2. Geometric mean IgE level was 9.76 i.u./ml; 33 subjects had levels falling

Figure 12.1: Distribution of total IgE level

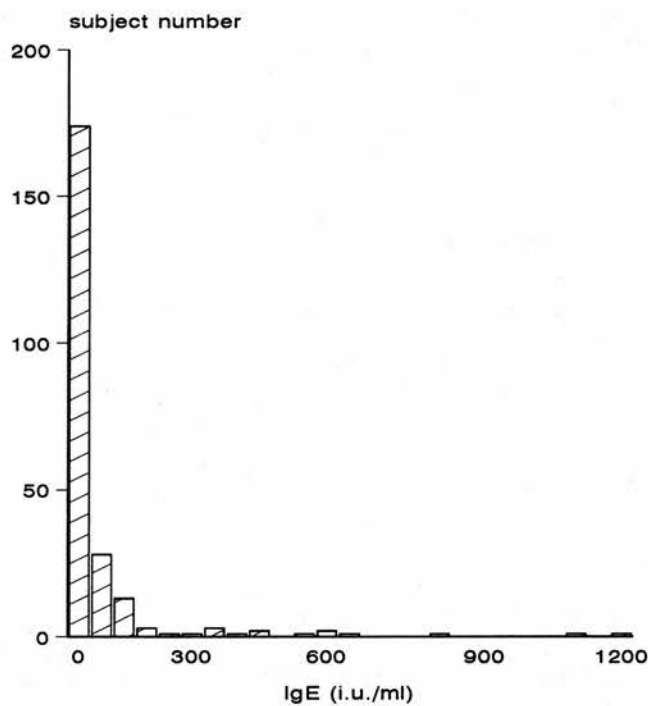
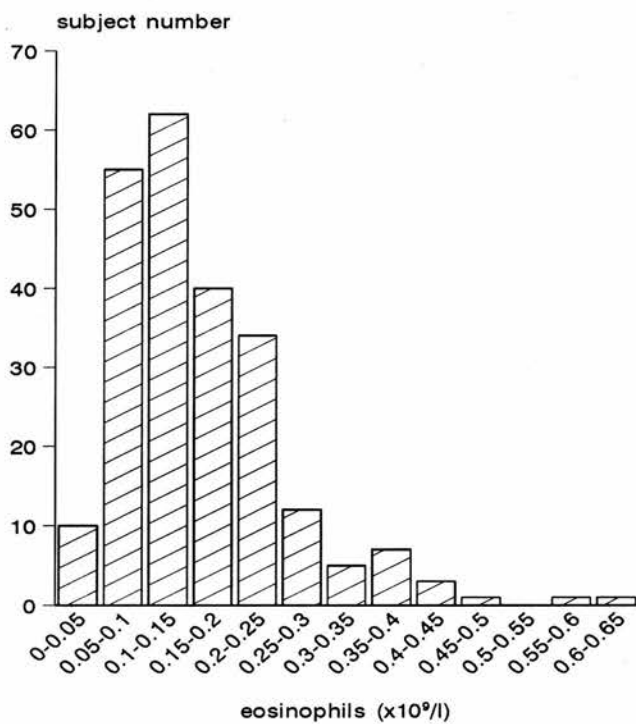


Figure 12.2: Distribution of eosinophil count



above the laboratory "normal" range (<100 i.u./ml). Geometric mean eosinophil count was $0.13 \times 10^9/l$; 6 subjects had counts above the "normal" range of $0.04 - 0.4 \times 10^9/l$.

Geometric mean IgE Z-score was higher in ex- than never-smokers (ex-smokers 1.0 [SD 8.1], never-smokers: 0.5 [SD 10.8]; $t=-2.1$, $p=0.04$), and in current than ex-smokers (current smokers 2.13 [8.6]; $t=-2.1$, $p=0.03$). There was also a dose-response relationship between packyears smoked and log IgE Z-score ($r=0.18$, $p<0.001$). Eosinophil count was not related to smoking habit. Subjects reporting a personal or family history of atopy did not have significant elevation of IgE or eosinophil Z-scores.

Subjects reporting asthma, bronchitis or asthma/bronchitis had higher geometric mean log IgE Z-scores than those with no diagnosis. However, the differences between the three diagnostic groups did not reach statistical significance (no diagnosis: 0.7 [SD 11.0], asthma: 2.5 [SD 6.3; $t=-2.8$, $p=0.01$], bronchitis: 1.7 [SD 6.7; $t=-2.4$, $p=0.02$], asthma/bronchitis: 2.1 [SD 5.6; $t=-2.6$, $p=0.01$]). Geometric mean log eosinophil Z-scores were higher in subjects reporting asthma and asthma/bronchitis than those without a diagnosis (no diagnosis: 0.8 [SD 8.6], asthma: 3.2 [SD 15.7; $t=-2.3$, $p=0.02$]; asthma/bronchitis: 2.5 [SD 7.9; $t=-1.9$, $p=0.04$]). In contrast, mean log eosinophil Z-scores of those reporting bronchitis were similar to those with no diagnosis (1.3 [SD 9.7]). Again, there were no significant differences between the three diagnostic groups.

Both IgE and eosinophil Z-scores were higher in symptomatic subjects, particularly those with cough or wheeze (Table 12.1).

In multiple regression analysis with baseline FEV_1 as the dependent variable, there was a significant independent negative relationship with eosinophil Z-score, but no relationship with IgE Z-score (Table 12.2). Over 60% of the variation in FEV_1 was explained by the independent variables ($R^2=0.61$).

Table 12.1: Measures of atopy in symptomatic and asymptomatic subjects

Symptom	Geometric mean IgE Z-score [SD]	Geometric mean eosinophil Z-score [SD]
Cough	2.2 [6.9]*	2.2 [10.0]*
No cough	1.6 [10.0]*	0.7 [8.5]*
Sputum	1.4 [9.3]#	1.6 [10.0]#
No sputum	0.8 [9.5]#	0.8 [8.7]#
Wheeze	1.6 [10.0]\$	1.6 [10.0]\$
No wheeze	0.7 [9.1]\$	0.7 [8.5]\$
Dyspnoea	1.7 [6.8]#	1.4 [12.6]
No dyspnoea	0.9 [10.0]#	0.9 [8.9]

*p<0.001; #p<0.05; \$p<0.01

Table 12.2: Factors associated with baseline FEV₁:
stepwise multiple regression analysis

Independent variables	Coefficient (B)	Standard error	p
Age	-0.033	0.004	<0.0001
Height	3.438	0.515	<0.0001
Packyears smoked	-0.008	0.002	<0.0001
Eosinophils Z-score	-0.091	0.036	0.01
IgE Z-score	-0.066	0.04	0.07
Sex*	0.348	0.099	0.0005

n=211, R² = 0.61

*female = 1, male = 2

To investigate whether the relationship between FEV₁ and eosinophils was different in subjects reporting asthma, an interaction term for reported asthma and eosinophil Z-score was included in the regression. This removed the significant relationship between eosinophils and FEV₁; the interaction term itself was negatively associated with FEV₁ (B=-0.074, SE=0.028, p=0.007).

Similarly, the addition of an interaction factor for the relationship between age and eosinophil count removed the independent association between eosinophils and FEV₁; again the interaction factor was negatively associated with FEV₁ (B=-0.001, SE=0.0005, p=0.0008). When regression analysis was performed separately for subjects aged <65 and ≥65 years, the negative relationship between eosinophils and FEV₁ was significant only in those aged ≥65 years (Table 12.3).

An interaction factor for the relationship between smoking (packyears) and eosinophils did not affect the results of the regression analysis, implying that the relationship between eosinophils and FEV₁ is not affected by smoking habit.

Multiple regression with log dose-response slope as the dependent variable showed an independent positive relationship between bronchial responsiveness and log IgE Z-score (Table 11.1). Addition of an interaction term for the association between reported asthma and IgE level did not alter the regression results; the relationship between IgE and bronchial responsiveness remained when subjects reporting asthma were omitted from the analysis.

Inclusion of an interaction term for age and IgE level removed the independent relationship between IgE and log DRS; the interaction term itself was significantly associated with log DRS (B=0.0025, SE=0.001, p=0.01). This suggested that the relationship between IgE and log DRS was stronger in older subjects; this was confirmed by separate analysis of younger and older subjects, which revealed that IgE was associated with bronchial responsiveness only in subjects aged ≥65 (Table 12.4).

The effect of smoking habit on the relationship between IgE and bronchial responsiveness was assessed by the inclusion of an interaction term for the relationship between IgE and packyears smoked. This did not alter the results of the regression analysis.

Table 12.3: Factors associated with baseline FEV₁ in older and younger subjects

	Age <65 b (p)	Age ≥65 b (p)
age	-0.04 (0.0001)	-0.03 (0.0004)
height	0.04 (<0.0001)	0.03 (0.0001)
packyears	-0.01 (0.04)	-0.01 (<0.0001)
eosinophils*	-0.05 (0.30)	-0.13 (0.007)
sex	0.32 (0.02)	0.39 (0.009)
IgE	-0.05 (0.40)	-0.08 (0.11)

Age <65: R²=0.48; age ≥65: R²=0.51

* log Z-score

Table 12.4: Factors associated with bronchial responsiveness in older and younger adults

	Age <65 b (p)	Age ≥65 b (p)
FEV1*	-0.56 (<0.0001)	-0.41 (<0.0001)
IgE#	0.13 (0.16)	0.30 (0.002)
sex	-0.19 (0.29)	-0.15 (0.45)
packyears	0.01 (0.14)	0.01 (0.24)
age	0.02 (0.31)	0.03 (0.15)
eosinophils#	-0.04 (0.66)	0.20 (0.05)

Age <65: R²=0.30; age ≥65: R²=0.25

* standardised residuals # log Z-score

Chapter 13: USE OF INHALED MEDICATIONS

Five hundred and six of the 508 subjects completing the full questionnaire answered the question "do you use inhalers ("puffers") for your chest?". Seventy-four subjects (14.5%) were using inhaled medications: 23 were using inhaled bronchodilators alone, and 51 were also using inhaled steroids. Four of those using inhalers were also taking oral steroids, two were also taking theophylline, and 2 were taking both oral steroids and theophylline. Only one subject was taking an oral beta agonist preparation.

More women than men used inhalers ($\chi^2=5.8$, $p=0.02$) (Figure 14.1), but there was no difference between older and younger adults ($\chi^2=2.6$, $p=0.1$) (Figure 14.2). Those taking oral steroids were older (age range 60-83 years, mean 73.0 years), as were those taking theophylline (age range 77-81 years, mean 79.8 years). The subject taking an oral beta-agonist was aged 58 years. There was no difference between the proportion of attenders and non-attenders using inhaled medications. Use of inhaled medications by smokers and non-smokers is shown in Figure 14.3. Although smokers were slightly more likely to be using inhalers, this difference was not significant.

Asthma or bronchitis was reported by all but 4 of the subjects using inhaled medications. However, only 70 (46.4%) of the 151 subjects reporting asthma or bronchitis were using inhalers. Subjects describing asthma or asthma/bronchitis were more likely to be using inhalers than subjects reporting bronchitis alone ($\chi^2=45.5$, $p<0.001$) (Figure 14.4). Although there was a tendency for increased use of inhaled steroids by those reporting asthma or asthma/bronchitis compared with those reporting bronchitis, this difference did not reach significance (asthma or asthma/bronchitis: 72.4% using inhaled steroids, bronchitis alone: 58.3% using inhaled steroids; $\chi^2=1.6$, $p=0.4$). Overall, 82.4% of inhaled bronchodilators plus steroids and 69.6% of bronchodilators alone were used by subjects reporting asthma.

Figure 13.1: Use of inhaled medications by women and men

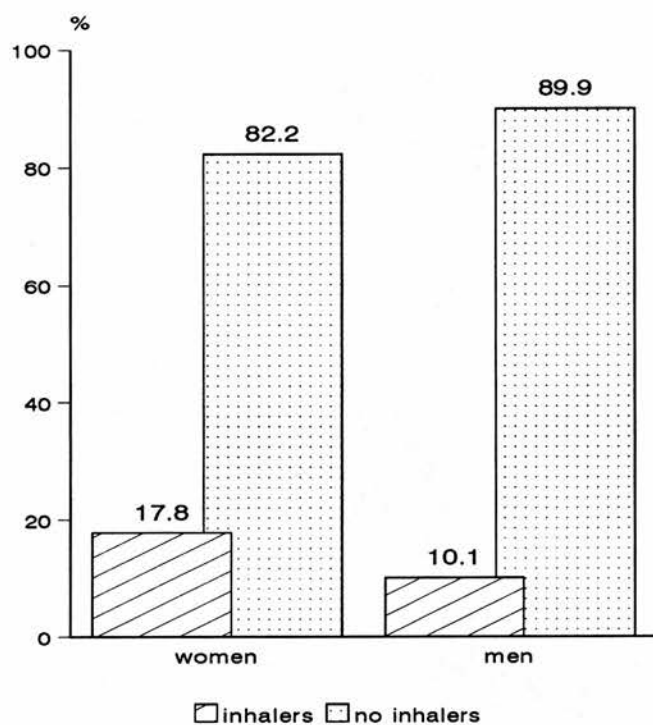


Figure 13.2: Use of inhaled medications by younger and older adults

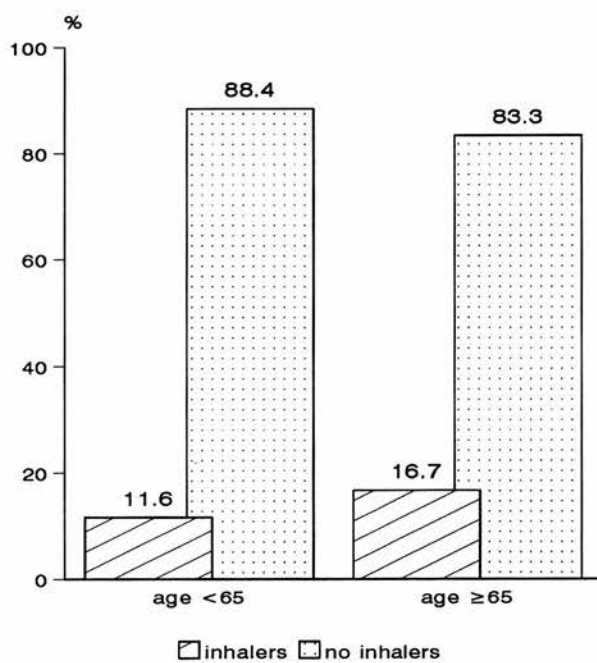


Figure 13.3: Use of inhaled medications by current, ex- and never-smokers

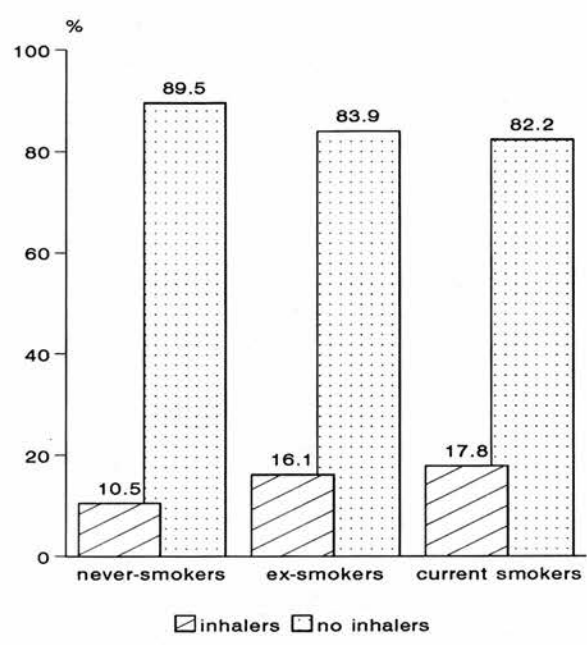
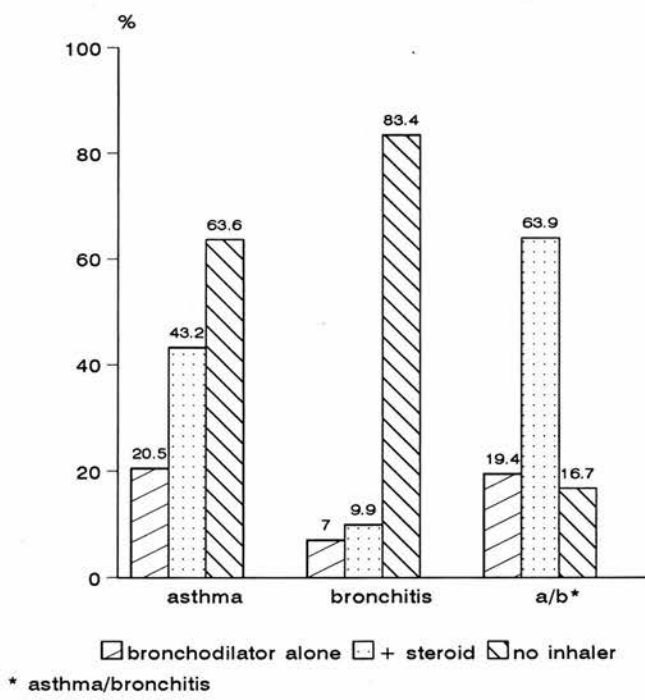


Figure 13.4: Use of inhaled medications by subjects reporting asthma, bronchitis and asthma/bronchitis



Inhaled medications were used more often by symptomatic subjects (figure 14.5). Only 2.2% of asymptomatic subjects reported used inhalers, compared with 10.5% of those with one respiratory symptom, 20.3% of those with two, 32.9% of those with three, and 54.6% with four symptoms ($\chi^2=98.4$, $p<0.001$). Breathlessness was the symptom most strongly linked with inhaler use. In subjects attending for bronchial challenge, 30.0% of those with symptoms of chronic bronchitis and 10.0% without were using inhalers ($\chi^2=12.5$, $p<0.001$); 37.5% of those with one or more symptom of bronchial irritability were using inhalers ($\chi^2=23.2$, $p<0.001$).

Subjects reporting wheeze were asked as part of the full questionnaire whether they had ever received treatment for this: 44.6% claimed to have been treated by their GP and 9.7% in hospital. Of those reporting treatment for wheeze (either by GP or in hospital), 63.1% were using inhaled beta-agonist \pm steroid.

Use of inhaled medications by subjects with chronic airflow obstruction is summarised in figure 14.6. Those with airflow obstruction were more likely to be using inhalers ($\chi^2=33.3$, $p<0.001$); however, over 60% of those with chronic airflow obstruction were not using inhaled medications. Treated subjects had more severe airflow obstruction (treated subjects: mean [SEM] $FEV_1/FVC\%=48.6\%$ [1.8], untreated subjects: 57.5% [0.7]; $t=5.3$, $p<0.001$). Seventy percent of subjects with chronic airflow obstruction who were not using inhaled medication described one or more respiratory symptoms.

Figure 14.7 shows inhaled medication use by subjects with bronchial hyper-responsiveness. Use of inhalers was more common in subjects with greater bronchial hyper-responsiveness ($\chi^2=10.0$, $p=0.007$). However, two thirds of those with greatly increased bronchial responsiveness and over three quarters of those with moderately increased bronchial responsiveness were not on inhaled therapy.

Figure 13.5: Use of inhaled medications by subjects with respiratory symptoms

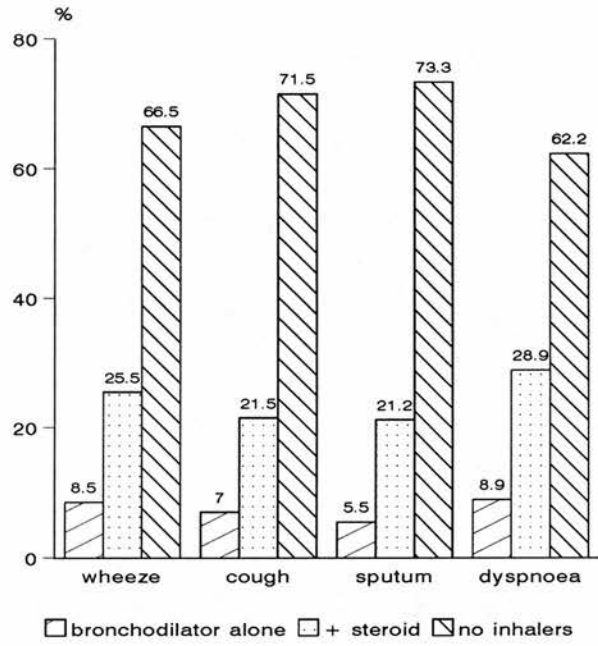


Figure 13.6: Use of inhaled medications by subjects with chronic airflow obstruction

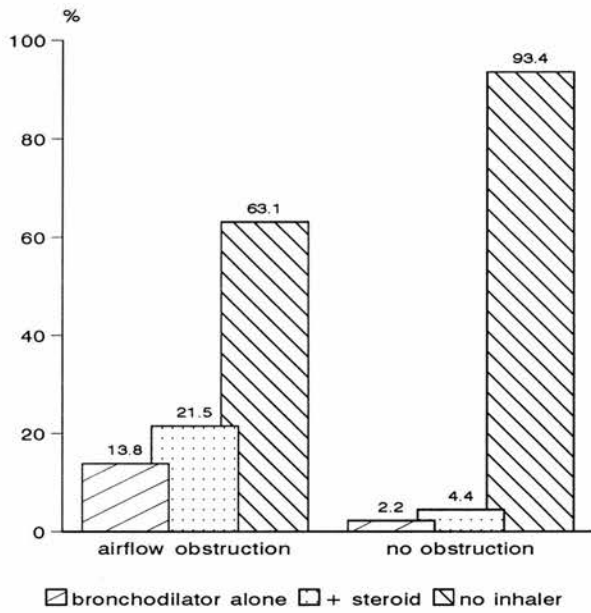
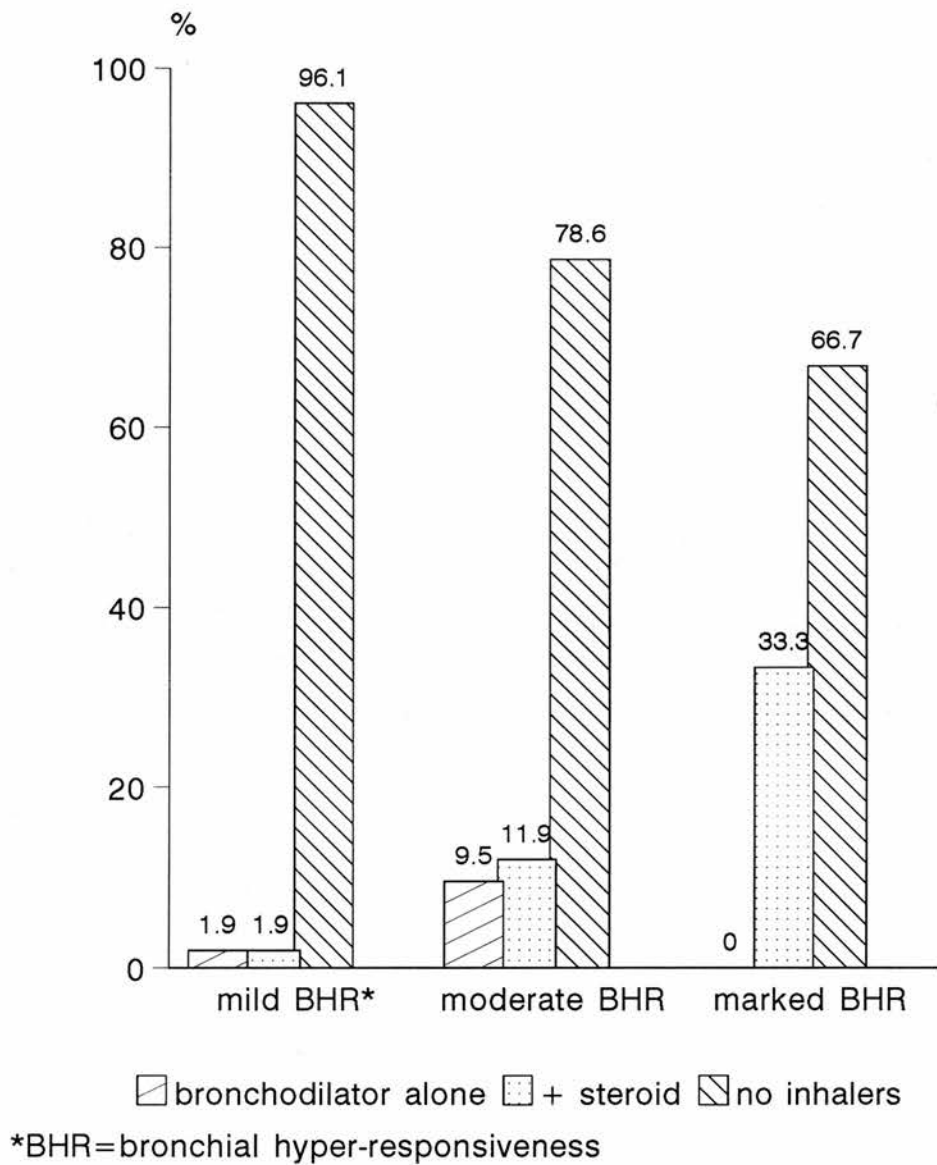


Figure 13.7: Use of inhaled medications by subjects with bronchial hyper-responsiveness



Chapter 14: QUALITY OF LIFE IN SUBJECTS WITH CHRONIC AIRFLOW
OBSTRUCTION AND BRONCHIAL HYPER-RESPONSIVENESS

(Renwick and Connolly, 1996b)

Studies in groups of patients with asthma and chronic airflow obstruction have shown that these illnesses have substantial impact on quality of life, impairing not only physical, but also psychological and social function (Guyatt et al. 1987; Schrier et al. 1990). However, the relationship between quality of life impairment and severity of airflow obstruction has generally been found to be weak (Guyatt et al. 1987; Quirk and Jones 1990; Schrier et al. 1990; Quirk et al. 1991). The effect of age on the relationship between quality of life and chronic airflow obstruction has not been examined, although some studies have suggested that the impact of obstructive airways disease on quality of life may be less in older subjects (Guyatt et al. 1987; Quirk and Jones 1990; Juniper et al. 1992).

i) Methods

Subjects attending for bronchial challenge completed the St George's Respiratory Questionnaire (Jones et al. 1992). This is a self-complete questionnaire designed for patients with asthma and chronic airflow obstruction, and validated in patients up to the age of 75 years. Separate scores are derived for 3 different components of quality of life: symptoms (frequency and severity), activities (causing or limited by breathlessness) and impacts (on employment and emotions, feelings of panic or control). The sum of these three scores represents the total quality of life score; this is expressed as a percentage of the total possible questionnaire score. Higher scores indicate greater morbidity; the maximum possible score is 100. Questions mostly take a "multiple-choice" format, and the questionnaire can be completed in approximately 10 minutes.

St George's Questionnaire scores were log transformed to achieve normal distribution. To allow log transformation of all scores, the value 0.5 was allocated to those subjects with scores of 0. Relationships between quality of life scores and pulmonary function were analysed by linear correlation and multiple regression. Subgroups were compared by grouped t test.

ii) Results

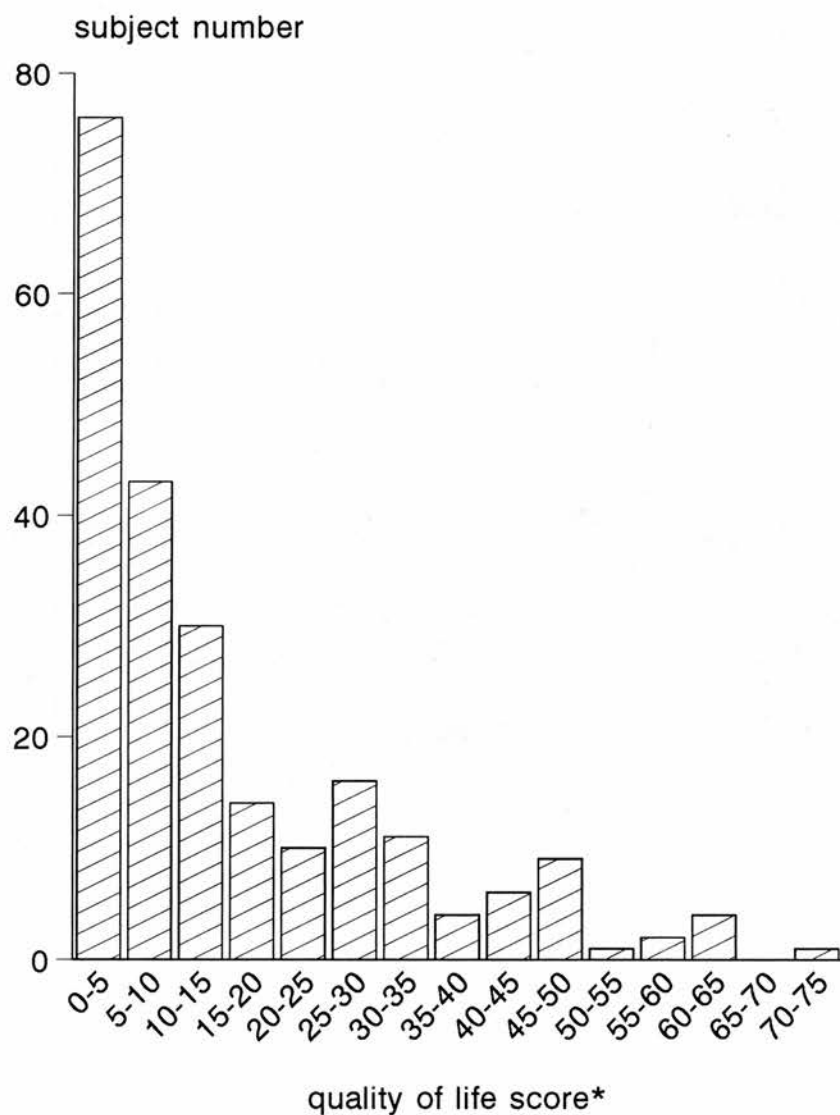
Two hundred and twenty-seven attenders performed reproducible spirometry and completed the St George's Questionnaire. Bronchial challenge results were available for 190 of these.

The distribution of total St George's Questionnaire scores is shown in Figure 15.1. Sixteen subjects had a score of zero (indicating no quality of life impairment), and geometric mean score was 8.5 (SD 3.5). Geometric mean quality of life scores were similar for men and women. There was no correlation between quality of life scores and age. However, the geometric mean Activities score was significantly higher for subjects aged ≥ 65 than for those < 65 years (age ≥ 65 : 11.0 [SD 5.1], age < 65 : 6.5 [SD 5.6; $t=-2.34$, $p=0.02$]).

Total quality of life scores were significantly higher (indicating greater quality of life impairment) in subjects with chronic airflow obstruction (table 15.1). Similarly, all quality of life scores except Impacts score were higher in those with bronchial hyper-responsiveness ($PD_{20} \leq 100\mu g$) (table 15.1).

There was significant linear correlation between total quality of life scores and both airways calibre and bronchial responsiveness (figures 15.2 and 15.3). Multiple regression analysis was performed with quality of life score as the dependent variable and baseline FEV_1 (expressed as standardised residuals), bronchial responsiveness (log dose-response slope), age and sex as independent variables. As there was significant correlation between baseline FEV_1 and log dose-response slope, an interaction term was included in the regression. This was not significantly related to quality of life in any of the analyses, and did not alter the value of R^2 . For the whole subject group, both total and separate component quality of life scores showed independent negative relationships with baseline FEV_1 . Only symptoms score showed a significant association with log dose-response slope (Table 15.2). The addition of baseline oxygen saturation and haemoglobin level to the regression failed to show significant relationships between these variables and quality of life.

Figure 14.1: Distribution of quality of life scores



*higher score indicates greater impairment

Table 14.1: Quality of life scores in subjects with and without chronic airflow obstruction or bronchial hyper-responsiveness

	TOTAL mean (sd)	ACTIVITIES mean (sd)	IMPACTS mean (sd)	SYMPTOMS mean (sd)
airflow obstruction	15.1 (3.1)	15.1 (4.5)	5.8 (5.4)	25.7 (3.6)
no obstruction	6.9 (3.4)	7.1 (5.6)	2.2 (4.9)	8.3 (5.9)
	t=-4.2 p<0.0001	t=-3.0 p=0.003	t=-3.9 p=0.0001	t=-4.5 p<0.0001
bronchial hyper- responsiveness*	9.5 (3.0)	10.7 (4.4)	2.5 (5.0)	16.2 (5.0)
no hyper- responsiveness	6.5 (3.2)	6.3 (5.4)	1.9 (5.0)	7.8 (5.5)
	t=-2.0 p=0.05	t=-1.9 p=0.05	t=-0.9 p=0.4	t=-2.6 p=0.01

*defined in text

Figure 14.2: Linear correlation between quality of life and airways calibre

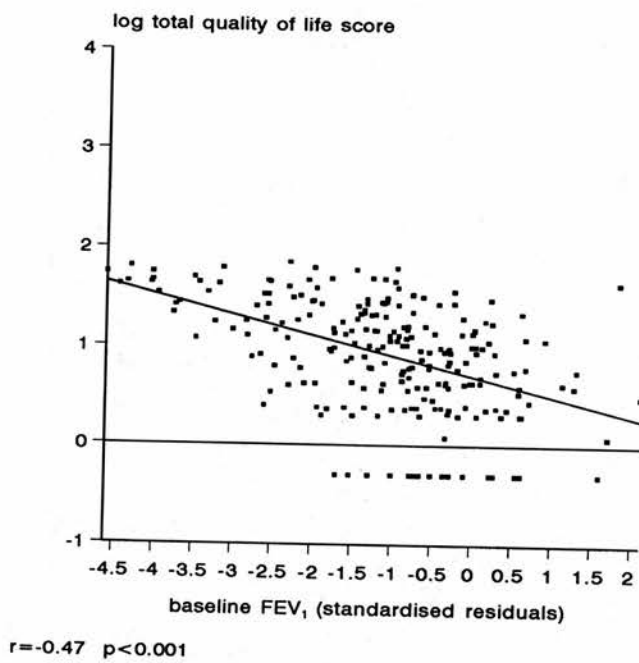


Figure 14.3: Linear correlation between quality of life and bronchial responsiveness

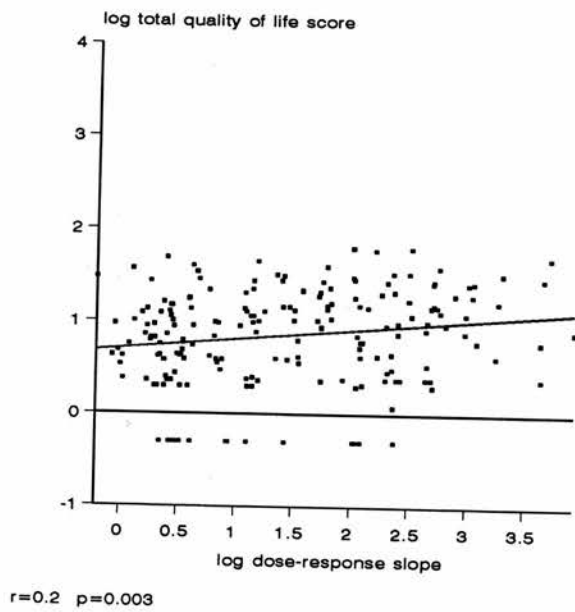


Table 14.2: Factors associated with quality of life scores:
stepwise multiple regression analysis

	TOTAL SCORE*	ACTIVITIES SCORE*	IMPACTS SCORE*	SYMPTOMS SCORE*
FEV1\$	B=-0.15 SE=0.04 p<0.0001	B=-0.18 SE=0.05 p<0.0006	B=-0.16 SE=0.05 p<0.002	B=-0.13 SE=0.06 p=0.03
bronchial responsiveness#	B=0.04 SE=0.04 p=0.3	B=0.06 SE=0.06 p=0.2	B=0.06 SE=0.05 p=0.3	B=0.11 SE=0.06 p=0.05
age	B=0.0003 SE=0.003 p=0.9	B=0.0003 SE=0.005 p=0.4	B=0.002 SE=0.004 p=0.7	B=-0.006 SE=0.005 p=0.2
sex	B=-0.05 SE=0.07 p=0.5	B=-0.16 SE=0.1 p=0.1	B=0.02 SE=0.01 p=0.8	B=0.10 SE=0.1 p=0.4

* log transformed values \$ standardised residuals # log dose-response slope
total: $R^2=0.08$ activities: $R^2=0.05$ impacts: $R^2=0.05$ symptoms: $R^2=0.07$

The effect of smoking on quality of life was assessed by comparing total St George's Questionnaire scores of smokers of <10 and ≥ 10 packyears. Quality of life was significantly impaired in smokers of ≥ 10 packyears (total score 11.7 [SD 3.8] vs 5.8 [SD 2.9]; $t=-3.3$, $p=0.001$). However, when smoking status (packyears smoked) was added to the multiple regression for the whole subject group, there was no independent relationship with total quality of life score. The addition of an interaction factor for smoking and airways calibre did not alter these results.

The effect of age on the relationship between quality of life and lung function was assessed by repeating the regression analysis separately for subjects aged <65 years and ≥ 65 years (table 15.3). This revealed differences between the age groups: in subjects aged <65 , total quality of life score was significantly associated with log dose-response slope but not baseline FEV_1 , whereas in the older group the opposite was true.

Table 14.3: Factors associated with quality of life scores
in older and younger adults

		Log total quality of life score
FEV1*	AGE < 65	B = -0.08 SE = 0.06 p = 0.2
	AGE ≥ 65	B = -0.18 SE = 0.05 p = 0.0005
bronchial responsiveness#	AGE < 65	B = 0.17 SE = 0.05 p = 0.0006
	AGE ≥ 65	B = -0.02 SE = 0.05 p = 0.62

Younger group: $R^2=0.15$; older group: $R^2=0.11$
 * standardised residuals # log dose-response slope

**Chapter 15: CHANGES IN OXYGEN SATURATION DURING
METHACHOLINE CHALLENGE**

(Renwick and Connolly, 1996c)

i) Methods

Oxygen saturation (SaO_2) was monitored during bronchial challenge using a finger oximeter (Biox 3700e, Ohmeda, Louisville, USA). The 95% confidence limits for background variability of SaO_2 in our laboratory (measured in young controls over 2 minutes) are $\pm 2.7\%$ (Zaidi et al. 1995). SaO_2 was observed to increase following spirometry, presumably secondary to a reduction in ventilation-perfusion mismatch resulting from repeated maximal inhalations. Consequently, all SaO_2 measurements were recorded immediately before each set of FEV_1 manoeuvres; this point was chosen arbitrarily. Multiple regression analysis was used to assess the influence of various parameters on oxygen saturation.

ii) Results

Baseline oxygen saturation was recorded in 238 subjects performing spirometry, and change in saturation was monitored during 208 methacholine challenges. Mean baseline SaO_2 was 96.8% (SD 1.6). Baseline SaO_2 was higher in women than men (women 97.0% ± 1.3 , men 96.5% ± 1.8 ; $t=2.2$, $p=0.03$).

There was no difference in baseline SaO_2 between subjects with or without a diagnosis of asthma or bronchitis. Baseline SaO_2 was lower in subjects with spirometric evidence of chronic airflow obstruction (airflow obstruction: 96.7% [SD 1.4], no obstruction: 97.1% [SD 1.2]; $t=3.2$, $p=0.002$). Subjects reporting one or more respiratory symptoms had lower baseline SaO_2 than asymptomatic subjects (symptomatic: 96.5% [SD 1.8], asymptomatic: 97.2% [SD 1.2]; $t=3.5$, $p=0.0005$).

Multiple regression analysis with baseline SaO_2 as the dependent variable showed an independent positive relationship with airways calibre (FEV_1 standardised residuals), and independent negative relationships with age and with packyears smoked (Table 16.1). Baseline SaO_2 was also independently associated with gender. Interaction factors for the relationships between age and packyears, and sex and packyears, did not alter the results. However, an interaction factor for the relationship between FEV_1 and packyears was strongly associated with baseline SaO_2 .

Table 15.1: Factors affecting baseline oxygen saturation

	Coefficient	SE	p value
FEV1 (standardised residuals)	0.45	0.08	<0.0001
AGE	-0.03	0.008	0.0003
PACK YEARS	-0.01	0.004	0.003
SEX	-0.42	0.19	0.03

No relationship was found between baseline saturation and bronchial responsiveness, haemoglobin, reported asthma or bronchitis, or respiratory symptoms
 $R^2=0.25$

Table 15.2: Factors affecting change in oxygen saturation

	Coefficient	SE	p value
% FALL IN FEV1	0.11	0.03	<0.0001
LOG METHACHOLINE DOSE	0.95	0.21	<0.0001
BASELINE SATURATION	0.35	0.14	0.01
FEV1 (standardised residuals)	-0.41	0.2	0.04

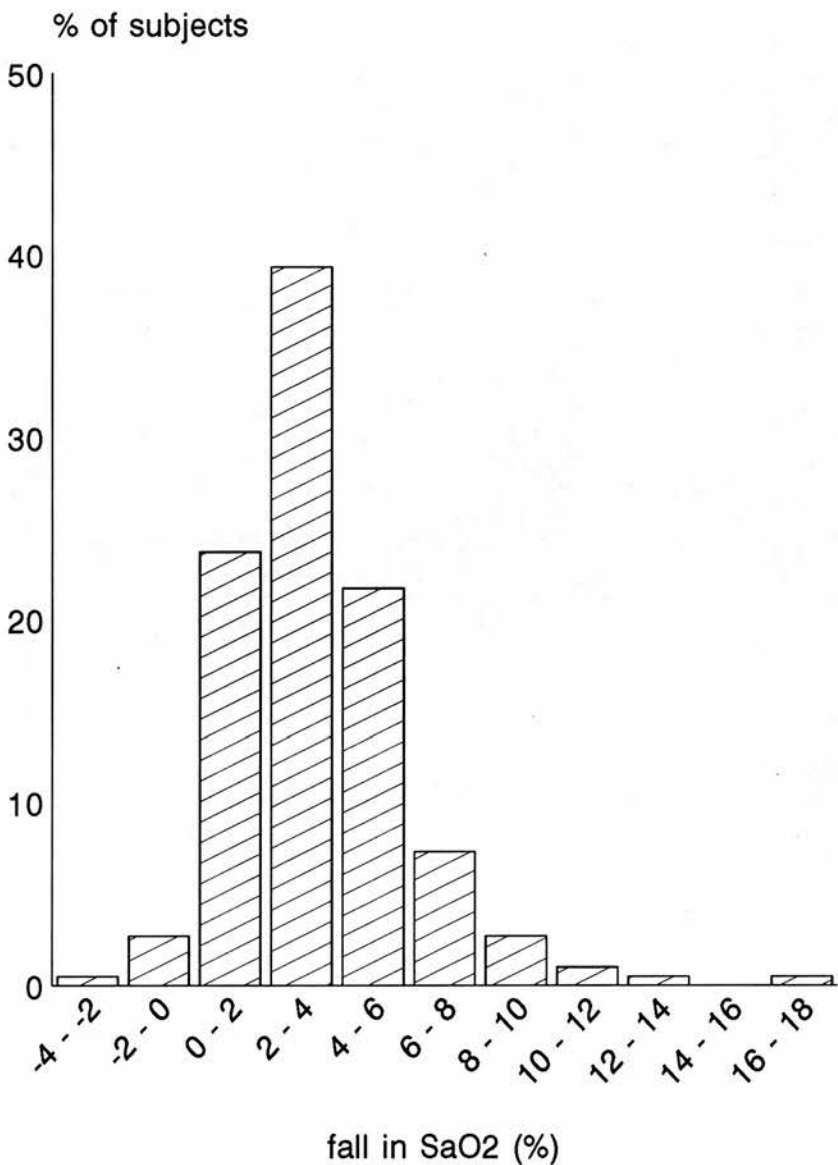
No relationship was found between fall in saturation and bronchial responsiveness (log DRS), age, sex, packyears, reported asthma/bronchitis, or respiratory symptoms
 $R^2=0.18$

($B=0.02$, $SE=0.002$, $t=8.9$, $p<0.0001$), removing the independent relationships of baseline SaO_2 with FEV_1 and packyears. The square of the coefficient of multiple regression (R^2) was 0.25.

Mean percentage fall in FEV_1 during bronchial challenge was 20.6% (SD 7.9); mean fall in SaO_2 was 3.2% (SD 2.4). Fall in SaO_2 was $>10\%$ in only 4 subjects (Figure 16.1), and was similar in subjects reporting asthma, bronchitis, and those with no reported diagnosis. There was no difference in the fall in SaO_2 between subjects with and without chronic airflow obstruction, or between symptomatic and asymptomatic subjects.

Multiple regression analysis showed fall in SaO_2 to be positively associated with baseline SaO_2 , % fall in FEV_1 , and log methacholine dose given (Table 16.2). Fall in SaO_2 was negatively associated with baseline FEV_1 (standardised residuals). R^2 was 0.16. Interaction factors for the relationships between fall in FEV_1 and log methacholine dose, and between baseline saturation and baseline FEV_1 were both significantly associated with fall in SaO_2 (fall in FEV_1 x log methacholine dose: $B=0.04$, $SE=0.007$, $t=5.6$, $p=0.008$; baseline SaO_2 x baseline FEV_1 : $B=-0.003$, $SE=0.002$, $t=-2.0$, $p=0.05$). Inclusion of these interaction factors removed the significant relationships of the individual determinants with fall in SaO_2 . R^2 was now 0.18. There was no relationship between fall in SaO_2 and age, sex, pack years, bronchial responsiveness, or haemoglobin.

Figure 15.1: Distribution of fall in oxygen saturation during methacholine challenge



Chapter 16: DISCUSSION

A) RESPONSE RATE

The response rate to our postal questionnaire was high, and compares favourably with other studies in this area (Dow et al. 1991; Horsley et al. 1993). Factors which may have contributed to this success include the use of GP's headed notepaper; repeated mailings for non-responders (which accounted for 46.0% of the total response); the "opt-out" slip allowing subjects to return the questionnaire without risk of being requested to attend hospital; simplification of the questionnaire sent to persistent non-responders; and tracing of non-responders by telephone or home visit (accounting for 6.2% of the total response).

Many subjects in the initial random sample were found to have left the area or died (93/893 subjects). Similar or higher prevalences of untraceable or deceased patients (10-20%) have been described in other studies taking information from GP records (Milne et al. 1971; Trigg et al. 1990). This seems to be an unavoidable consequence of using such data. Screening of selected subjects by GPs prior to inclusion in the study was necessary to ensure GP co-operation with the study. It was reassuring that the majority of subjects thought unsuitable by GPs met the agreed exclusion criteria.

We are confident that responders were representative of the selected population in terms of age and sex. Population statistics for this area suggest that women are over-represented in our population (Office of Population Censuses and Surveys 1991); the high proportion of men amongst subjects initially selected but found to be ineligible may be responsible for this difference.

Persistent non-responders were younger than responders, and contained a higher proportion of males. This may reflect increased mobility of the younger male population. In contrast, subjects refusing to participate were older, and more likely to be women. Difficulties in persuading older people, particularly women, to participate in research projects have been previously described (Cochrane 1954; Milne et al. 1971; Bakke et al. 1990), although one study found higher response rates in subjects aged > 85 than in those aged 65-74 years (Rockwood et al. 1989).

Differences in health status have also been reported between responders and non-responders in epidemiological surveys. Different studies have found responders either more or less likely to use medical services than non-responders (Milne et al. 1971; Rockwood et al. 1989). Non-smokers, asthmatics, and middle-aged women have been over-represented in some epidemiological surveys of bronchial responsiveness (Burney et al. 1987; Trigg et al. 1990; Britton et al. 1994a). In the current study, very few asthmatics were found in the non-responders contacted by telephone or visit. This suggests that our estimate of the prevalence of reported asthma may be slightly high. Conversely, bronchitis was reported by a relatively large number of contacted non-responders, and so our estimate of the prevalence of reported bronchitis may be slightly low. However, the high questionnaire response rate means that these effects would be small.

Furthermore, subjects reporting asthma were more likely, and those reporting bronchitis less likely, to complete the full (rather than the abbreviated) questionnaire. This could in theory have led to over-representation of asthmatics in the group attending for bronchial challenge. However, reported asthma, bronchitis and respiratory symptoms were all equally common in attenders and non-attenders, confirming that the attenders were a representative group.

Over half of our responder population was aged ≥ 65 years, as were over 40% of those performing bronchial challenge. This is the highest proportion of older adults included in a population study of bronchial responsiveness (except for studies including only elderly subjects (Dow et al. 1991; Horsley et al. 1993)). In all other published population studies, less than 15% of those included have been in this age group. The inclusion of this high proportion of elderly people may have aided the detection of the subtle relationship between bronchial responsiveness and age, and the persistence of the relationship between bronchial responsiveness and atopy in the elderly.

The very high prevalence of current and ex-smoking in Central Manchester is noteworthy. Our "current smoker" figures are higher than General Household Survey estimates for this region (Office of Population Censuses and Surveys 1991b). However, there was a particularly high prevalence of current smoking in the non-responders contacted by telephone or visit; if these are representative of the remaining non-responders, our estimate of smoking prevalence may still be low. Smokers have been under-represented in some other population studies of bronchial responsiveness (Burney et al. 1987; Britton et al. 1994a). These high levels of smoking probably reflect the nature of this relatively deprived inner-city population; our results are likely to be representative of the urban Caucasian population elsewhere in Britain.

The low attendance rate for bronchial challenge was disappointing. Older people were particularly reluctant to take part, resulting in a small age difference between attenders and non-attenders. Attendance rates of less than 50% have been described in several other epidemiological surveys of bronchial responsiveness (Table 2.4) (Mortagy et al. 1986; Trigg et al. 1990; Higgins et al. 1993). However, the fact that reported asthma/bronchitis, respiratory symptoms, smoking habit and use of inhaled medications were all similar in our attenders and non-attenders confirms that we have studied a representative sample of the responder population.

In the interests of safety in this elderly random population sample, we excluded subjects with symptomatic ischaemic heart disease or ECG abnormalities from bronchial challenge. However, methacholine challenge has been performed in patients with symptomatic cardiac failure (Cabanès et al. 1989), and published guidelines suggest that only those within 3 months of myocardial infarction, or with uncontrolled hypertension should be excluded (Sterk et al. 1993).. In total, 16.7% of responders were excluded on these grounds.

The exclusion of subjects with low baseline FEV₁ from bronchial challenge is accepted practice (Sterk et al. 1993). In our study 10.5% of attenders were excluded

for this reason. Four percent of adults were unable to complete bronchial challenge. These figures are comparable with other published epidemiological surveys (Table 2.4). The vast majority of adults attending for bronchial challenge were able to perform spirometry reproducible to within $\pm 10\%$; this contrasts with a study of elderly adults in which 14% failed to produce results within $\pm 5\%$ (Dow et al. 1992b). The fact that so few subjects ($< 5\%$) were unable to complete bronchial challenge supports the assertion that this technique is practical even in elderly populations (Connolly et al. 1988b).

B) REPEATABILITY OF BRONCHIAL CHALLENGE

Repeatability of bronchial challenge is dependent on both subject and technique-related factors (Sterk et al. 1993; Weeke et al. 1987). Careful standardisation of the challenge protocol, calibration of nebuliser output and the performance of all tests by a single operator increases repeatability (Ryan et al. 1981a; Britton et al. 1986; Chinn et al. 1987). Subjects with previous experience of the bronchial challenge technique produce more repeatable results than inexperienced subjects (Knox et al. 1991).

In general, most published studies have found repeatability of bronchial responsiveness to be within 1-3 doubling doses of challenge agent (Weeke et al. 1987; Sterk et al. 1993), with better results being obtained in small selected groups than in larger epidemiological surveys (Ryan et al. 1981b; Chinn et al. 1987; Higgins et al. 1988). In one study, subjects with "obstructive lung disease" ($FEV_1 < 80\%$ predicted or past history of airflow obstruction) had lower reproducibility than healthy subjects (Bakke et al. 1991a).

Other studies of repeatability of the Newcastle Dosimeter method of bronchial challenge have been published. In a group of 20 asthmatic subjects with reproducible baseline FEV_1 and previous experience of bronchial challenge, 95% limits of agreement for repeated measurements were 0.5-2.0 x initial PD_{20} for both methacholine and histamine (Connolly et al. 1988a). Subsequent studies in older subjects (aged 65-82) showed poorer, although still acceptable, repeatability for $PD_{20}(FEV_1)$ (95% limits of agreement 0.39-2.57 x initial reading) (Connolly et al. 1988b). A comparison of the Newcastle dosimeter technique with the Wright nebuliser tidal breathing method in 20 asthmatic subjects found superior repeatability for the Newcastle dosimeter method (95% limits of agreement 0.3-3.0 x initial PD_{20}) (Beach et al. 1993). These values are comparable with those for the current study (95% limits of agreement 0.4-2.7 x initial reading).

Our results confirm that repeatability is better in younger than older subjects.

However, the two age groups in the current study are not strictly comparable: the younger group were hospital personnel (mostly medical and nursing staff), and so might be expected to be more familiar with spirometry than the older subjects recruited at random from the population. A decrease in repeatability with increasing age could result either from greater variability in spirometry performance by older subjects, or from an intrinsic variability in the response to methacholine.

We have shown that using the mean of 3 FEV₁ recordings produces more repeatable results than does the best of 3. This may be because the mean is less affected by the "deep breath bronchodilatation" that occurs as a result of performing repeated spirometry (Orehek et al. 1981; Beach et al. 1993). Our results also suggest superior reproducibility for FEV₁ than for PEFR or FEF₅₀. This confirms published studies comparing bronchial challenge results using FEV₁ and PEFR (Connolly et al. 1988b), or FEV₁ and FEF₅₀ (Dehaut et al. 1983).

Two other studies have shown lower reproducibility of DRS(FEV₁) in subjects not achieving a PD₂₀ (Seppala 1991; Trigg et al. 1994), and several authors have expressed concern that repeatability of DRS may be unsatisfactory in subjects with low levels of bronchial responsiveness (Cockcroft and Berscheid 1983; Higgins et al. 1989a; Chinn et al. 1992). This may be the result of log transformation of calculations based on small changes in FEV₁, which will magnify the effect of within-subject variation and random technical errors.

This observation limits the application of DRS in the laboratory setting. However, the use of DRS allows the inclusion of data from many more subjects than have a calculable PD₂₀. In the context of epidemiological surveys or large cross-sectional study designs, where repeated testing of the same subjects is not planned, this latter advantage may outweigh the disadvantage of reduced reproducibility at lower levels of bronchial responsiveness. In our population, the difference between repeatability in those with and without a calculable PD₂₀ was small, and repeatability was within 2 doubling doses in both groups.

C) PREVALENCE OF REPORTED ASTHMA, BRONCHITIS AND RESPIRATORY SYMPTOMS

The questionnaire used in the current study was designed specifically for this study, but used questions about respiratory symptoms and diagnosed asthma similar to those included in other widely used and well validated questionnaires (Medical Research Council 1960; Ferris 1978; Burney and et al. 1989). Using Cohen's kappa statistic to assess agreement between postal and interview responses showed slightly lower agreement than reported for comparisons between two interview-administered questionnaires (Abramson et al. 1991). This may reflect the fact that more subjects reported one or more symptoms on the postal questionnaire than at interview, which confirms the findings of other comparisons between postal and interview questionnaires (Toren et al. 1993). Agreement was lowest for breathlessness, which is perhaps the most difficult of these symptoms to define, due to its dependence on level of exertion (ie speed of walking, incline of hill).

The classification of subjects reporting both asthma and bronchitis is difficult. This problem has been encountered in other studies, and probably reflects the lack of clear diagnostic criteria for asthma and chronic bronchitis (see page 33). Inclusion of subjects reporting both diagnoses as either "asthma" or "bronchitis" substantially increases reported disease prevalence (from 7.3% to 14.6% for asthma, and from 15.4% to 22.7% for bronchitis).

In the Tucson study, 46% of patients aged >65 years reporting asthma also reported chronic bronchitis, and 63% reported emphysema (Burrows et al. 1991). Those with asthma/emphysema were mostly male heavy smokers, and the authors classified them as "non-asthmatic"; those with asthma/bronchitis were classified as "asthmatic" (Burrows et al. 1991). However, in the current study, subjects reporting asthma/bronchitis appear to be a distinct group, differing from those reporting either asthma or bronchitis alone. Thus, asthma/bronchitis was more common in women, but asthma alone and bronchitis alone were equally common in both sexes. Furthermore, although the strong relationship of reported asthma/bronchitis with

current smoking resembles that of bronchitis alone, the high prevalence of bronchial hyper-responsiveness in the group reporting asthma/bronchitis is more similar to those with asthma alone. Given this overlap, it is not surprising that this group has received multiple diagnostic labels.

It is possible that subjects reporting asthma/bronchitis may represent smokers who initially had asthma, but have subsequently developed concurrent smoking-related airflow obstruction. This would account for the presence of features of both asthma and chronic bronchitis in these individuals. If these subjects with asthma/bronchitis are regarded as a separate group, then the prevalence of self-reported asthma in Central Manchester falls within the range reported by most other studies (see table 2.5), but reported bronchitis is still more common than elsewhere. Alternatively, including asthma/bronchitis with the group reporting asthma alone gives a higher prevalence of reported asthma than that found in other populations. The diagnosis of emphysema was reported only rarely in Central Manchester; this may reflect local diagnostic practices, and a reluctance to use a term which the public associates with poor prognosis.

Respiratory symptoms were reported more frequently in Central Manchester than in other published studies (table 2.6). Although the prevalence of one or more symptoms was similar (53.8% in Central Manchester, 30-60% in other studies (Dow et al. 1991; Horsley et al. 1991; Lundback et al. 1991; Viegi et al. 1991a)), individual symptoms were all more common in our population than in several others (Milne 1978; Samet et al. 1982; Rijken et al. 1987; Woolcock et al. 1987; Krzyzanowski et al. 1990; Viegi et al. 1991a; Peat et al. 1992a; Isoaho et al. 1994a). Perhaps significantly, the only other study reporting levels of reported cough and sputum similar to the current study was a survey performed in Glasgow (Milne 1978); this may reflect similarities between the populations of these two large industrial cities. Prevalences of breathlessness similar to that found in Central Manchester have been reported by the Tucson study (Lebowitz et al. 1975), and by a recent Dutch population survey (Boezen et al. 1995).

The prevalence of respiratory symptoms in the current study was higher than that of reported asthma or bronchitis. This finding is particularly surprising for chronic bronchitis, which is a diagnosis based purely on the presence of symptoms. In the current study, only 39.0% of subjects reporting bronchitis fulfilled MRC criteria for this diagnosis, and only 49.0% of those fulfilling the diagnostic criteria reported having bronchitis. Our terminology ("bronchitis" rather than "chronic bronchitis") is unlikely to account for this discrepancy, which has been noted by others (Lebowitz et al. 1975; Lundback et al. 1991).

Our data show no change in the prevalence of reported asthma or bronchitis with increasing age. Both increasing and decreasing prevalences have been suggested by other studies (Lebowitz et al. 1975; Lundback et al. 1991; Neukirch et al. 1995). Others have also suggested that symptom frequency increases with age (Lebowitz et al. 1975; Burr et al. 1979; Mortagy et al. 1986; Rijken et al. 1987; Lundback et al. 1991; Viegi et al. 1991a); again, our results do not support these findings.

We have also found no evidence of higher prevalence of reported asthma in women than men, or of reported bronchitis in men than women, as has been reported by others (Samet et al. 1982; Schachter et al. 1984; Isoaho et al. 1994b). However, reported asthma/bronchitis was more common in women than men in the current study. Our results confirm differences found in other populations between symptoms reported by men and women; sputum production was more common in men, and breathlessness in women (Caird and Akhtar 1972; Milne and Williamson 1972; Lebowitz et al. 1975; Burr et al. 1979; Krzyzanowski et al. 1990; Isoaho et al. 1994a).

The strong link between smoking and reported bronchitis is expected, and confirms other reports (Samet et al. 1982; Lundback et al. 1991). However, the relative lack of current smokers in subjects reporting asthma is interesting, and may suggest that smokers receiving a diagnosis of asthma are more likely to give up smoking. If so, this would represent another manifestation of the "healthy smoker effect" (see page

59). However, those reporting asthma/bronchitis had smoking habits resembling those reporting bronchitis, rather than those reporting asthma.

The relationship between symptom prevalence and smoking habit in our population again confirms previous reports (Milne and Williamson 1972; Samet et al. 1982; Rijken et al. 1987; Horsley et al. 1991; Lundback et al. 1991; Viegi et al. 1991a; Menezes et al. 1994). However, the stronger relationship between symptoms and smoking habit in younger than older adults has not been previously described. The reason for the higher prevalence of symptoms in older never-smokers, and lower symptom reporting by older current smokers is unclear. Many older adults in Central Manchester have lived in the same urban area for many years; chronic exposure to an environmental agent (eg airborne pollution) could be implicated in the production of symptoms independent of smoking (Viegi et al. 1991a). Under-reporting of respiratory symptoms by older smokers has been noted in another population study (Lundback et al. 1993a).

Although we have found respiratory symptoms to be more common in subjects with increased bronchial responsiveness, over one quarter of those with bronchial hyper-responsiveness were asymptomatic. High prevalences of asymptomatic bronchial hyper-responsiveness have been previously noted in both young and older populations (Kolnaar et al. 1995; Rijken et al. 1987). However, the significance of an asymptomatic increase in bronchial responsiveness is unclear (see page 49). The relationship between bronchial hyper-responsiveness and respiratory symptoms in our population is further discussed on page 190.

D) RESULTS OF SPIROMETRY

A decline in pulmonary function with age is accepted, and most studies suggest linear relationships between FEV_1 , FVC, FEV_1/FVC and age (Cotes 1993). Our figures confirm these relationships, although the correlation was weaker for $FEV_1/FVC\%$ than for other spirometric parameters. This is partly the result of an increase in FEV_1/FVC in women over the age of 85, which may represent the reluctance of less robust subjects in this age-group to take part. Alternatively, it may be the result of "survival of the fittest": poor lung function is a marker of increased mortality from various causes, and so subjects surviving into the older age groups are likely to be those with better lung function (Cook et al. 1989).

The detrimental effect of smoking on lung function is undisputed (Dockery et al. 1988). We have confirmed significantly lower FEV_1 and $FEV_1/FVC\%$ in women smokers, but have failed to show a difference in men. This is surprising, and suggests either unexpectedly low FEV_1 in never-smoking men, or unexpectedly high FEV_1 in smokers. Alternatively, it may represent a survival effect: the increased mortality of male smokers with airflow obstruction may have falsely increased the mean FEV_1 of smoking men in this relatively elderly population. Smoking appeared to have little effect on FVC in either women or men; this finding is in agreement with other population studies (Burrows et al. 1977; Miller et al. 1986).

Further assessment of our results has been made by comparison with 5 reference ranges, derived from the results of other cross-sectional population surveys by regression analysis (Cotes 1993). Reference equations are calculated separately for men and women; the effect of smoking on lung function is accounted for by excluding smokers, or by producing separate equations for smokers and never-smokers. Since the decision of an individual whether or not to start or give up smoking may be influenced by his or her lung function and/or the presence of symptoms, exclusion of all smokers from the analysis may introduce bias into the reference population (Cotes 1993).

Several reference ranges for lung function have been published from the 1960s onwards, representing studies of various different populations (Cotes 1993). Composite equations have also been calculated, combining the results of different studies (Quanjer 1983). However, the relevance of studies performed 30 years ago in predicting lung function in the 1990s is debatable. Environmental changes over time may cause lung function to be affected by year of birth; this has been termed a "cohort effect" (Cotes 1993). Furthermore, some studies have included both smokers and non-smokers, whereas others have excluded not only smokers but also those with respiratory symptoms (table 8.1). Few reference ranges have included subjects over a wide age-range such as that included in the current study; extrapolation of results from younger to older subjects assumes a constant rate of decline in FEV_1 with age, and is probably not valid. In one study, values of FEV_1 measured longitudinally differed considerably from values predicted by a cross-sectional analysis of the same population, and it has been suggested that reference ranges calculated from a study of one particular population cannot give accurate predictions for another (Burrows et al. 1986).

Comparison of measured FEV_1 in Manchester never-smoking men and women with values predicted by the published reference ranges identifies some important differences. Measured values are similar to reference ranges predicted by Cotes et al (who included smokers in their population) (Cotes et al. 1966) and Burr et al (who did not exclude symptomatic subjects or those with asthma or chronic bronchitis) (Burr et al. 1985). However, more recent studies which have excluded both smokers and symptomatic subjects have produced higher predicted values; comparison of asymptomatic never-smoking Manchester men and women with these shows significantly lower lung function in the Manchester population (Dockery et al. 1985; Roberts et al. 1991; Enright et al. 1993). The reason for this is unclear; it may reflect environmental exposure (for example to airborne pollution), or result from general poor health in the Central Manchester population. It may also represent a cohort effect, perhaps following exposure of this adult population to high levels of ambient air pollution in childhood (in the 1920s-1940s). The fact that this

difference is more marked in men than women raises the possibility that a work-related factor may be involved; unfortunately, comprehensive occupational histories were not taken in the current study.

Alternatively, the difference may merely reflect differences in population selection: the study by Roberts et al was based on volunteers rather than a random population sample (Roberts et al. 1991), and Enright et al incorporated particularly stringent screening to ensure that only healthy subjects were included (Enright et al. 1993). However the Central Manchester population attending for spirometry excluded subjects with ischaemic heart disease, and removal of symptomatic subjects from the analysis failed to remove the difference between measured and predicted lung function.

E) PREVALENCE OF CHRONIC AIRFLOW OBSTRUCTION AND INCREASED BRONCHIAL RESPONSIVENESS

We have found high prevalences of both chronic airflow obstruction (26.4%), and moderately/greatly increased bronchial responsiveness ($PD_{20} \leq 100\mu\text{g}$ methacholine; prevalence=26.0%). This level of bronchial responsiveness has been shown to have a positive predictive value for symptomatic asthma of almost 100% in young populations (Cockcroft et al. 1985). Comparison with other studies suggests that both chronic airflow obstruction and increased bronchial responsiveness are more common in Central Manchester than in other populations (table 2.7, 2.8).

However, comparisons between studies are hampered by the use of different definitions of chronic airflow obstruction and bronchial hyper-responsiveness. Two studies have used a similar definition of chronic airflow obstruction to the current study, and both report a lower prevalence (12.5% (Isoaho et al. 1994a), and 18.2% (Peat et al. 1990); Central Manchester 26.4%). $PD_{20} \leq 800\mu\text{g}$ was found in 6% of the population of Hordaland (Bakke et al. 1991a), and 51.0% of Central Manchester adults; no other authors have reported the prevalence of $PD_{20} \leq 100\mu\text{g}$, but $PD_{20} \leq 200\mu\text{g}$ was reported in 12% adults over 65 in the New Forest (Horsley et al. 1993), and in 23% adults in Surrey (Trigg et al. 1990), compared with 34.6% in Manchester.

Our data confirms a strong inter-relationship between bronchial responsiveness and baseline airways calibre. Although this relationship has previously been reported to be stronger in subjects with chronic airflow obstruction than in those with asthma (Woolcock et al. 1991), we found it to be strongest in those with the most marked increase in bronchial responsiveness ($PD_{20} \leq 12.5\mu\text{g}$).

Other studies have suggested that chronic airflow obstruction is more common in men (Isoaho et al. 1994a) and bronchial hyper-responsiveness in women (Rijken et al. 1987; Cerveri et al. 1988; Trigg et al. 1990; Carrozzi et al. 1992; Peat et al. 1992a). Our data supports neither of these associations; sex was not independently

associated with bronchial responsiveness in multiple regression analysis. Furthermore, chronic airflow obstruction has been found to be more common in older people (Krzyzanowski et al. 1986; Peat et al. 1990; Isoaho et al. 1994a). Although our data confirms this finding, the difference did not reach statistical significance, perhaps because of a type II error. Simple categorical analysis also showed no relationship between age and bronchial responsiveness in our population.

We have found a strong relationship between smoking and chronic airflow obstruction, as described in other populations (Peat et al. 1990; Isoaho et al. 1994a). However, the prevalence of chronic airflow obstruction in never-smokers is higher in the current study than in other populations (Central Manchester 12.8%; Finland 2%; Busselton 7% (Peat et al. 1990; Isoaho et al. 1994a)). The increased frequency of bronchial hyper-responsiveness in current smokers has also been previously reported (Kabiraj et al. 1982). Ex-smokers in the current study had levels of bronchial responsiveness similar to those of never-smokers, suggesting that the effects of smoking on bronchial responsiveness may be short-lived, although bronchial hyper-responsiveness has been shown to persist for at least 3 months after giving up smoking (Buczko et al. 1984).

Respiratory symptoms were more common in subjects with chronic airflow obstruction and those with increased bronchial responsiveness than in other subjects. As expected, chronic productive cough was the symptom most strongly related to chronic airflow obstruction, whilst wheeze and breathlessness were more predictive of moderately and greatly increased bronchial responsiveness. However, the predictive values of these symptoms for either chronic airflow obstruction or bronchial hyper-responsiveness was low. This concurs with other population studies, which have found that up to 50% of subjects with airflow obstruction reported neither symptoms nor a diagnosis (Peat et al. 1990; Isoaho et al. 1994a), and that over 50% of bronchial hyper-responsiveness may be asymptomatic (Rijken et al. 1987; Kolnaar et al. 1995). Like others, we have found that questions about diagnosed asthma have higher positive predictive value for bronchial hyper-

responsiveness than questions about symptoms (Dales et al. 1987; Enarson et al. 1987).

The significance of asymptomatic chronic airflow obstruction and bronchial hyper-responsiveness is unclear. It has been suggested that airflow obstruction may remain asymptomatic until a relatively advanced stage, or alternatively that symptoms of chronic airflow obstruction may develop insidiously and be tolerated by patients. Denial of symptoms by smokers has been reported in a questionnaire study (Lundback et al. 1993a). Asymptomatic bronchial hyper-responsiveness may represent asymptomatic, pre-clinical or quiescent asthma, or may be the temporary result of viral infection or exposure to an inhaled allergen or irritant. Despite the apparent increase in tolerance of methacholine-induced bronchoconstriction in older adults (Connolly et al. 1992a) we have not shown higher prevalence of asymptomatic bronchial hyper-responsiveness in older subjects. However, our data confirms the finding of others that symptoms of "bronchial irritability" are not strongly associated with increased bronchial responsiveness in older adults (Dow et al. 1992b; Horsley et al. 1993).

The low prevalence of diagnosed asthma or bronchitis amongst subjects with chronic airflow obstruction or bronchial hyper-responsiveness may represent failure of patients to report symptoms to their doctors, or failure of doctors to investigate or treat these. Reluctance of geriatricians to perform spirometry in elderly people with respiratory symptoms was described in a small questionnaire study (Ghosh et al. 1992).

Because of doubts about the significance of asymptomatic bronchial responsiveness, it has been proposed that asthma should be defined as bronchial hyper-responsiveness plus appropriate symptoms (Toelle et al. 1992). Using this definition gives a prevalence of asthma in Central Manchester of 15.0%. This is still higher than the prevalence of reported asthma, but similar to that of asthma plus asthma/bronchitis.

The very high prevalences of chronic airflow obstruction and bronchial hyper-responsiveness in the Central Manchester population are consistent with the finding of lower than predicted levels of FEV_1 . As discussed above, factors such as relative poverty in childhood (leading to poor diet and over-crowding, and increasing the risk of viral respiratory tract infection and passive cigarette smoke exposure), exposure to high levels of ambient air pollution, and occupational exposure may all be implicated.

F) USE OF MULTIPLE REGRESSION ANALYSIS TO INVESTIGATE FACTORS ASSOCIATED WITH BRONCHIAL HYPER-RESPONSIVENESS

Several of the factors potentially affecting bronchial responsiveness are inter-related (for example airways calibre and age or smoking habit); multiple regression analysis allows assessment of the joint influence of these variables, taking into account the correlations between them.

i) Baseline airways calibre, smoking, age and sex

Multiple regression confirms the strong relationship between baseline airways calibre and bronchial responsiveness suggested by analysis with bronchial responsiveness expressed as a categorical variable. This relationship has been found in many other population surveys (van der Lende et al. 1973; Malo et al. 1983; Burney et al. 1987; Kennedy et al. 1990; Trigg et al. 1990; Bakke et al. 1991a; Peat et al. 1991, 1992b; Horsley et al. 1993; Britton et al. 1994a; Sparrow et al. 1994). Possible mechanisms of the association between airways calibre and bronchial responsiveness have been discussed above (page 53).

Multiple regression analysis failed to show an independent effect of smoking on bronchial responsiveness in the current study, despite the fact that analysis with bronchial responsiveness expressed as a categorical variable suggested increased prevalence of bronchial hyper-responsiveness in current smokers (see chapter 10). This suggests that smoking does not affect bronchial responsiveness directly, but indirectly via its effects on airways calibre. Inclusion of airways calibre in regression analysis has been shown to eliminate the relationship between smoking and bronchial responsiveness in other population studies (Kennedy et al. 1990; Trigg et al. 1990; Rijken et al. 1993a; Britton et al. 1994a) (page 58).

Studies of the relationship between bronchial responsiveness and sex have provided conflicting results; where a difference has been found, this has usually been increased bronchial responsiveness in women (page 58). Our results do not support

a difference in bronchial responsiveness between women and men.

More interesting is our finding of a positive relationship between bronchial responsiveness and age, although this accounts for only 3% of the population variation in bronchial responsiveness. Other published population surveys have disagreed on the presence or absence of such a relationship, which may have been obscured by the small numbers of older adults included in most other studies (page 57). In the current study, the relationship between age and bronchial responsiveness was only apparent in analysis of the entire population, and was not seen when older and younger subjects were examined separately.

A second factor allowing our demonstration of a relationship between age and bronchial responsiveness may have been the expression of pre-challenge airways calibre as standardised residuals to remove age and sex-bias. Other studies have either failed to take airways calibre into account, or have included FEV_1 , % predicted FEV_1 , or FEV_1/FVC , all of which retain age and sex bias. The residual age bias associated with the use of these parameters may have obscured the relationship between age and bronchial responsiveness.

An increase in bronchial responsiveness with age is biologically plausible; several of the abnormalities in the beta-adrenergic system seen in asthmatics are similar to changes occurring as part of the normal ageing process (see page 27). Measurement of both bronchial responsiveness and beta-adrenoceptor density and function in a longitudinal study of older adults would be necessary to confirm an association between increasing bronchial responsiveness and decreasing beta-adrenoceptor function with increasing age.

ii) Atopy

Our results show an association between airways calibre and eosinophil count. This confirms the results of other population surveys (van der Lende et al. 1969; Burrows et al. 1980, 1983, 1988; Kauffman et al. 1986; Vollmer et al. 1986; Frette

et al. 1991; Annesi et al. 1992). Only one population study has failed to show a relationship between airways calibre and measures of atopy: this study excluded asthmatic individuals (O'Connor et al. 1993). Removal of subjects reporting asthma eliminated the relationship between FEV₁ and eosinophil count in both the current study and another population study (Kauffman et al. 1986). This suggests a role for eosinophil-mediated airways inflammation in the development of chronic airflow obstruction in asthmatics. We have found no evidence of a relationship between airways calibre and total IgE, although such a relationship has been reported in some populations (Burrows et al. 1980, 1983, 1988; Kauffman et al. 1986; Vollmer et al. 1986; Frette et al. 1991; Annesi et al. 1992). The very high value of R² for the regression equation with FEV₁ as the dependent variable is worthy of note: over 60% of the variation in FEV₁ in our population can be explained on the basis of variation in age, sex, height, packyears smoked and measures of atopy.

Our results also show a relationship between bronchial responsiveness and IgE level, but not eosinophil count. Other population studies have also reported associations between bronchial responsiveness and IgE (Carrozzi et al. 1992), eosinophils (Rijken et al. 1993a), or both (O'Connor et al. 1989a; Parker et al. 1990), although some have contradicted this (Annesi et al. 1988, 1992; Bakke et al. 1991a). The relationship between IgE and bronchial responsiveness in the current study was independent of reported asthma.

We have not shown a change in the association between measures of atopy and baseline airways calibre or bronchial responsiveness with increasing smoking habit. This suggests that atopic mechanisms are involved in the pathogenesis of chronic airflow obstruction and bronchial hyper-responsiveness both smokers and non-smokers. Thus our data does not support the theory that bronchial hyper-responsiveness in smokers with chronic airflow obstruction is merely the consequence of reduced airways calibre (Ramsdale and Hargreave 1990). Although our results confirm that total IgE is elevated in smokers (Taylor et al. 1985a; Vollmer et al. 1986; O'Connor et al. 1989b; Dow et al. 1992a; Jensen et al. 1992),

we have failed to show an interaction between the effects of atopy and smoking on FEV₁, as suggested by others (Orie et al. 1961; O'Connor et al. 1989a; Dow et al. 1992a). Several authors have also reported eosinophilia in current smokers (Taylor and Luksza 1987; O'Connor et al. 1989b; Tollerud et al. 1991); this was not the case in our population.

The raised serum IgE and eosinophils in subjects reporting asthma confirms expectations (Kauffman et al. 1986; Burrows and et al. 1989), and has been noted even in elderly asthmatics (Burrows et al. 1991). Elevated IgE levels and eosinophil counts in subjects describing respiratory symptoms have also been previously reported (Weiss et al. 1984; Mensinga et al. 1990; Barbee et al. 1991; Tollerud et al. 1991). However, we have been unable to confirm links between different symptoms and different measures of atopy. It is interesting that reported atopy was not associated with raised IgE or eosinophils in this population. Results of skin tests, IgE and eosinophil counts showed only weak correlation with questionnaire reports of allergy in another study (Burrows et al. 1980).

Our finding that measures of atopy are more strongly associated with airflow obstruction and bronchial responsiveness in older than younger adults is surprising, and contradicts accepted teaching. Other studies of older adult populations have shown relationships between IgE and airways calibre (Dow et al. 1992a) and between IgE, eosinophils and bronchial hyper-responsiveness (O'Connor et al. 1989a). However, the prevalence of positive skin tests decreases with age (Skassa-Brociek et al. 1987), and two population surveys have shown a decline in the association between skin test positivity and bronchial hyper-responsiveness with increasing age (Burney et al. 1987; Higgins et al. 1993).

It is possible that the effect of atopy on lung function has a "U-shaped" association with age, being stronger in children/younger adults (not included in the current population) and in the elderly than in "middle-aged" adults. The small numbers of elderly people included in other studies may have obscured this relationship. Our

results suggest that atopic mechanisms should not be overlooked as a significant factor in older adults with asthma or chronic airflow obstruction.

H) USE OF INHALED MEDICATIONS

Few epidemiological surveys of obstructive airways disease have considered use of medication. Those that have suggest that many subjects with symptoms or spirometric evidence of airflow obstruction are untreated (Banerjee et al. 1987). Surveys of medications used by nursing home residents have shown low numbers using bronchodilators (Nolan and O'Malley 1989; Hatton 1990).

A general practice-based study in the North of England found that 5% of the population aged 0 to >85 years was using inhalers (Roberts and Bateman 1994). This is lower than the prevalence of inhaler use in our population, perhaps because of the different age ranges involved. The use of inhalers by patients with a respiratory diagnosis was similar in both studies (Northern region 38%, Central Manchester 46.4%), although fewer subjects with bronchitis were treated in the Northern region (6%, vs 16.9% in Central Manchester). In the Northern region, inhalers were more commonly used by men and by patients aged less than 70; these findings were not confirmed by the current study. This may relate to differences in either disease prevalence or diagnostic criteria between the two study populations. It may be significant that there were wide (up to two-fold) variations in rates of diagnosed asthma and bronchitis between separate general practices within the Northern region, which were unlikely to reflect variations in actual disease prevalence (Roberts and Bateman 1994).

Over half of the subjects in our population reporting asthma or bronchitis, and over half with proven chronic airflow obstruction were not using inhaled drug therapy. Although those using inhalers had more severe airflow obstruction and bronchial hyper-responsiveness, 70% of untreated subjects with airflow obstruction described respiratory symptoms. We do not know, however, how many of these untreated subjects had reported their symptoms to a doctor. Thus, the low use of inhalers in this population may reflect either tolerance of respiratory symptoms by patients, or therapeutic nihilism by their GPs.

Subjects reporting a diagnosis of asthma or asthma/bronchitis were more likely to be using inhaled medications than those reporting bronchitis alone. This seems appropriate, since those reporting asthma or asthma/bronchitis had a higher prevalence of bronchial hyper-responsiveness, which may imply better response to treatment (Connolly et al. 1988b). The use of oral steroids more frequently in older than younger asthmatics has been previously reported (Bailey et al. 1992). The very small number of patients receiving theophylline in this population is surprising; this may reflect poor patient compliance or local prescribing habits.

D) QUALITY OF LIFE IN SUBJECTS WITH CHRONIC AIRFLOW OBSTRUCTION AND BRONCHIAL HYPER-RESPONSIVENESS

Our results confirm that obstructive airways disease impairs quality of life. We have found no independent relationship between quality of life and age, sex, or smoking status but have shown significant relationships with baseline FEV₁ and with bronchial responsiveness. However, the value of R² for the multiple regression calculations was low, indicating that variation in lung function explains only a small amount of the variation in quality of life, as previously reported (Guyatt et al. 1987; Quirk and Jones 1990; Schrier et al. 1990; Quirk et al. 1991; Malo et al. 1993; Ketelaars et al. 1996). Psychological assessment of patients with obstructive airways disease has shown that illness attitudes and beliefs are stronger predictors of breathlessness and exercise tolerance than are measures of airflow obstruction (Morgan et al. 1983; King and Cotes 1989; Jones 1991). Quality of life was associated with partial pressure of oxygen in a small group of patients with severe chronic obstructive pulmonary disease, but an independent relationship with oxygen saturation was not found in the current study (Okubadejo et al. 1996).

The St George's Questionnaire has not been validated in a general population sample, or in subjects aged >75 years (Jones et al. 1992). In the current study, some subjects with no airways disease recorded very little quality of life impairment, producing a skewed distribution of scores. The lack of correlation between quality of life scores and age in the current study suggests that the questionnaire is valid in the elderly. However, the mean Activities score was higher for older subjects, indicating reduced activity levels with age.

It has been suggested that the quality of life impairment associated with obstructive airways disease decreases with increasing age (Guyatt et al. 1987; Quirk and Jones 1990; Quirk et al. 1991; Juniper et al. 1992). It has also been shown that older adults describe less severe acute symptoms than younger adults when exposed to the same degree of methacholine-induced bronchoconstriction (Connolly et al. 1992a).

However, there is no evidence for a general decrease in the reporting of distressing chronic symptoms by the elderly: indeed the opposite may be true (Woods and Britton 1985). The results of the current study do not confirm a reduction in the impact of obstructive airways disease on quality of life in older people.

Our results show that quality of life is associated with bronchial responsiveness in adults aged <65 , but with baseline FEV_1 in older adults. The reasons for this difference are not clear. Increased bronchial responsiveness is associated with symptoms of "bronchial irritability" in young adults but not the elderly (Mortagy et al. 1986; Dow et al. 1992b); the lack of these symptoms may diminish the effect of increased bronchial responsiveness on quality of life. Alternatively, our results may reflect a change in the interaction between baseline FEV_1 and bronchial responsiveness with age, rather than a change in their interaction with quality of life.

J) CHANGES IN OXYGEN SATURATION DURING METHACHOLINE CHALLENGE

Previous smaller studies have shown a relationship between the change in oxygenation during nonspecific bronchial challenge and either the change in FEV₁ (Baldini et al. 1991; van Broekhoven et al. 1991; Fontana et al. 1993), the dose of challenge agent inhaled (Reed and Calhoun 1991), the pre-challenge level of oxygenation (Rodriguez-Roisin et al. 1991), or none of these parameters (Poppius and Stenius 1977). In the current study we have shown that the change in saturation is related to all of the above parameters, as well as the baseline FEV₁. However, the low coefficient of multiple regression indicates that only 18% of the variation in SaO₂ is attributable to the measured parameters, and so other unidentified factors must be involved.

No other study of oxygen saturation during bronchial challenge has included adults with chronic airflow obstruction. Asthma and chronic bronchitis might be expected to have different effects on oxygen saturation, but we found no difference during methacholine challenge between subjects reporting these diagnoses. However, subtle differences might be detected using a more sensitive technique for the measurement of oxygenation.

Monitoring of saturation is relatively insensitive in well oxygenated subjects because of the sigmoid shape of the oxygen saturation curve (West 1990). However, use of this technique during bronchial challenge gave similar results to measurement of partial pressure of oxygen (PtcO₂) using a transcutaneous electrode in one study (Hoffarth et al. 1990), but not another (Wilson et al. 1991). Similarly, measurement of PtcO₂ during bronchial challenge gave comparable results to direct measurement of partial pressure of oxygen (PaO₂) in arterial blood samples (Dal Negro and Allegra 1989). Almost all studies of SaO₂ during bronchial challenge have shown a statistically significant mean fall in SaO₂ of around 3%, which is consistent with the results of the current study (Poppius and Stenius 1977; Burke et al. 1989; Dal Negro and Allegra 1989; Stewart et al. 1989; Wilson et al. 1991).

The fact that the fall in SaO_2 during bronchial challenge is not related only to fall in FEV_1 but also to methacholine dose suggests that methacholine may be altering SaO_2 both indirectly, via reduction in airways calibre, and also directly, by some other mechanism. Such mechanisms could include alteration of ventilation-perfusion distributions, as have been recorded during nonspecific bronchial challenge (Rodriguez-Roisin et al. 1991). For example, methacholine-induced vasodilation in poorly ventilated areas of lung could reduce oxygen saturation.

We had hoped to identify baseline factors which could be used to identify subjects at risk of hypoxia during methacholine challenge. However, although fall in SaO_2 is associated with baseline FEV_1 (confirming the expectation that subjects with chronic airflow obstruction may become hypoxic during methacholine challenge), there is also a positive association with baseline SaO_2 . This unexpected relationship has been previously noted in a study of PaO_2 during methacholine challenge in asthmatic patients (Rodriguez-Roisin et al. 1991), and may represent a form of regression to the mean.

Elderly subjects in our population, despite having lower baseline FEV_1 and oxygen saturation, were not at increased risk of desaturation during methacholine challenge. This reinforces the assertion that nonspecific bronchial challenge with methacholine is a safe and useful technique in this age group (Connolly et al. 1988b). A fall in SaO_2 with increasing age has been previously reported (Sorbini et al. 1968; Blom et al. 1988), but was not demonstrated in adults aged >65 years with chronic bronchitis (Delclaux et al. 1994). However, it is not clear whether our results can be extrapolated to subjects excluded from the study, for example those with baseline $\text{FEV}_1 < 60\%$ predicted or with ischaemic heart disease.

Chapter 17: SUMMARY

- (1) A random sample of 893 white adults aged ≥ 65 years was selected from local GP lists using random number tables. Of these, 110 were found to have moved away, died, or were excluded from the study (exclusions: non-Caucasian, housebound, confusion, other major illness). The remaining 783 were sent a questionnaire; 723 responded (response rate 92.3%). Responders were representative in terms of age and sex. Smoking was very common in this population (29.2% current and 37.3% ex-smokers).
- (2) Twenty-two percent of responders were excluded from bronchial challenge (exclusions: ischaemic heart disease, oral steroids, beta-blockers or anticholinergic medication). Two hundred and forty-six attended and performed reproducible spirometry (62.5% of those invited; 31.5% of eligible population). Attenders were slightly younger than non-attenders, but were representative in terms of sex, smoking habit, reported asthma and bronchitis, and prevalence of respiratory symptoms.
- (3) Methacholine challenge was performed using the Newcastle dosimeter technique. Nebulisers were calibrated by direct measurement of output using a fluoride tracer impacted onto filter papers. Repeatability of methacholine challenge results was within 2 doubling doses.
- (4) Prevalence of reported asthma was 7.3%, bronchitis 15.4%, and a further 7.3% reported both asthma and bronchitis ("asthma/bronchitis"). Subjects reporting asthma/bronchitis showed similarities both to those reporting asthma (high prevalence of bronchial hyper-responsiveness) and to those reporting bronchitis (strong association with current smoking). These subjects may represent asthmatics who have developed smoking-related lung disease. If they are regarded as asthmatic then reported prevalence of asthma in this population exceeds that of other populations. The prevalence of reported bronchitis is higher in Central Manchester whether or not those with asthma/bronchitis are included.
- (5) One or more respiratory symptoms were reported by 53.8% of subjects. This is comparable with other populations, but prevalences of individual symptoms were higher in Central Manchester than in most other studies.
- (6) Neither reported diagnoses nor symptoms were more common in older subjects,

and both were equally common in women and men. Smokers were more likely to report bronchitis, asthma/bronchitis or symptoms than never-smokers; in contrast, few subjects reporting asthma were current smokers.

(7) The relationship between smoking and symptom prevalence was stronger in younger than older adults. This was the result of a lower prevalence of symptoms in older than younger smokers, and a slightly higher prevalence of symptoms in older than younger never-smokers. Possible reasons for this include under-reporting of symptoms by elderly smokers, a cohort effect (eg exposure of older adults to adverse environmental or occupational factors in younger life, leading to respiratory symptoms even in non-smokers), or reduced survival of symptomatic smokers into older age.

(8) As expected, FEV_1 , FVC and FEV_1/FVC showed a linear decline with age. Women smokers had lower FEV_1 than never-smokers; however, there was no difference in spirometry results between smoking and never-smoking men.

(9) Comparison of measured FEV_1 with values predicted by reference equations derived from published cross-sectional surveys showed that measured values were significantly lower than those predicted by 2 of 5 reference equations in women, and by 3 of 5 equations in men.

(10) Chronic airflow obstruction was present in 26.4% of the population (22.9% of those aged ≤ 65 , and 29.7% of those aged ≥ 65 years). This prevalence is higher than that reported for other populations. Only 44.6% of subjects with airflow obstruction reported a diagnosis of bronchitis and/or asthma, although three quarters (76.6%) reported one or more respiratory symptoms. Chronic airflow obstruction was equally common in men and women, and in older and younger adults. There was a strong association with smoking: only 15.4% of those with airflow obstruction had never smoked.

(11) Mildly increased bronchial responsiveness was found in 25.0% of subjects tested; a further 26.0% had levels of bronchial hyper-responsiveness compatible with asthma ($PD_{20} \leq 100\mu g$). Increased bronchial responsiveness was more common than has been reported in other populations. Categorical analysis showed no difference in the prevalence of bronchial hyper-responsiveness between women and

men, or between older and younger adults.

(12) Increased bronchial responsiveness was more common in current smokers; ex-smokers had levels of bronchial responsiveness similar to those of never-smokers. There was no increase in the prevalence of bronchial hyper-responsiveness in subjects reporting bronchitis alone; however, subjects reporting asthma and asthma/bronchitis had significantly higher prevalence. The positive predictive value of reported asthma for bronchial hyper-responsiveness was 77.8%.

(13) Although symptoms (particularly breathlessness and wheeze) were more common in subjects with bronchial hyper-responsiveness, 26.4% of subjects with $PD_{20} \leq 100 \mu g$ were asymptomatic. Symptoms of bronchial irritability were not particularly strongly associated with bronchial hyper-responsiveness in this population.

(14) Multiple regression analysis with bronchial responsiveness as the dependent variable and age, gender, baseline airways calibre, smoking status and measures of atopy as independent variables revealed an independent negative relationship between bronchial responsiveness and airways calibre, and independent positive relationships with age and total IgE level.

(15) The relationship between bronchial responsiveness and age explained only 3% of the population variation in bronchial responsiveness. This association has not been found consistently in other populations, perhaps because of the small proportion of elderly individuals included in other studies.

(16) The relationship between bronchial responsiveness and IgE has been previously reported, and was found both in subjects reporting asthma and in non-asthmatics. This suggests that IgE-mediated processes are involved in the pathogenesis of increased bronchial responsiveness.

(17) Multiple regression analysis with baseline FEV_1 as the dependent variable and age, gender, height and measures of atopy as independent variables identified an independent relationship between airways calibre and eosinophil count. This was abolished by removal from the analysis of subjects reporting asthma. Eosinophil-mediated inflammatory processes may be involved in the development of airflow obstruction in asthmatics.

(18) Relationships between IgE and bronchial responsiveness, and between eosinophils and airways calibre were stronger in older than younger adults. This contradicts suggestions that atopy plays no part in the pathogenesis of asthma in the elderly.

(19) Inhaled medications (bronchodilators \pm steroids) were used by only 46.4% of those reporting asthma or bronchitis. Subjects reporting bronchitis were less likely to be using inhaled medications than those reporting asthma. Only 36.9% of those with chronic airflow obstruction, and 54.7% of those with $PD_{20} \leq 100\mu g$ were using inhaled medications.

(20) Quality of life (assessed by a disease-specific quality of life questionnaire) was significantly impaired in subjects with chronic airflow obstruction and increased bronchial responsiveness. Both baseline airways calibre and bronchial responsiveness were significant predictors of quality of life impairment.

(21) Changes in oxygen saturation during bronchial challenge were small, and were not higher in older subjects or those with airflow obstruction.

(22) The reasons for the high prevalence of reported asthma and bronchitis, respiratory symptoms, chronic airflow obstruction and bronchial hyper-responsiveness, and for the lower-than-predicted FEV_1 in this random population sample are not clear. Possible explanations include childhood experience of overcrowding, poor nutrition, exposure to high levels of ambient pollution, occupational factors, and/or high prevalence of smoking.

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APPENDIX 1: POSTAL QUESTIONNAIRE

BRONCHIAL RESPONSIVENESS AND ASTHMA STUDY

QUESTIONNAIRE

Please answer the following questions by putting a tick next to the answers that apply to you.

EXAMPLE: Have you ever had..... HAY FEVER?
DERMATITIS?
ECZEMA?

1. PERSONAL DETAILS.

Name: _____

Date of birth: _____

Sex: _____

Can we contact you by telephone?.....YES/NO

Telephone number: _____

2. PREVIOUS HEALTH.

Have you ever been treated by your doctor for any serious illness in the past?.....YES/NO

If yes, please give details: _____

Have you ever been treated for any of the following.....ASTHMA?

BRONCHITIS?

EMPHYSEMA?

ANY CHEST CONDITION?

When was this? _____

Have you ever had HEART TROUBLE?.....YES/NO

If yes, please give details:_____

3.MEDICATIONS.

Do you take any medications or tablets prescribed
by your doctor?YES/NO

If yes, please list them here:_____

Do you use inhalers ("sprays" or "puffers") for
your chest?YES/NO

If yes, please list them here:_____

Do you take any medications or tablets bought
from the chemist?YES/NO

If yes, please list them here:_____

4. SMOKING.

Have you ever been a smoker?.....YES/NO

If you are CURRENTLY a smoker: How much do you smoke?

_____ cigarettes per day

_____ cigars per week

_____ ounces tobacco per week

How old were you when you started smoking?_____

If you are an EX-smoker:

How old were you when you started smoking?_____

How old were you when you stopped?_____

On average, how much did you used to smoke?

_____ cigarettes per day

_____ cigars per day

_____ ounces tobacco per week

5. OCCUPATION

What is or was your main occupation?_____

6.ALLERGIES

Are you allergic to anything?.....YES/NO

If yes,please give details:_____

Have you ever hadHAY FEVER?
DERMATITIS?
ECZEMA?

7.FAMILY HISTORY

Does anyone in your family suffer from
.....HAY FEVER?
ASTHMA?
ALLERGIES?
ECZEMA?

If so,please give details:_____

8.COUGH/PHLEGM ("flem")/SPUTUM ("spit")

Do you have a cough?.....YES/NO

If yes,do you cough mostly.....AT NIGHT?
IN THE MORNING?
AT ANY TIME?

How long have you had the cough?_____

Do you cough up phlegm ("flem" or "spit") from
your chest?.....YES/NO

9.BREATHLESSNESS

Do you get breathless at night?.....YES/NO

Do any of the following activities make you
breathless:

.....WALKING UPHILL?

WALKING ON THE LEVEL?

WALKING AROUND THE HOUSE?

TALKING?

SITTING AT REST?

10.WHEEZE AND CHEST TIGHTNESS

Does your chest ever sound wheezy or "whistling"
when you breathe?.....YES/NO

Does your chest ever feel "tight"?..... YES/NO

Have you ever needed treatment for wheezing or
chest tightness:

.....BY YOUR DOCTOR?

AT HOSPITAL?

11.CHEST COLDS

If you get a cold,does it go to your chest?

.....YES/NO

If yes,how often has this happened in the last
year?_____

THANKYOU FOR COMPLETING THE QUESTIONNAIRE

APPENDIX 2: LETTERS SENT TO SUBJECTS

1. Explanatory letter accompanying postal questionnaire
2. First reminder
3. Second reminder and abbreviated questionnaire
4. Appointment confirmation

MANCHESTER CENTRAL HOSPITALS AND COMMUNITY CARE NHS TRUST

THE ROBERT BARNES MEDICAL UNIT

The Robert Barnes Medical Unit
Barnes Hospital
Kingsway, Cheadle SK8 2NY

Tel No :- 061 - 491 - 2300
Fax No :- 061 - 491 - 4479

Dear

We are doctors working in the Manchester Royal Infirmary. We are setting up a research study on Asthma, and hope that you may be able to help. We have discussed this study with your General Practitioner, who has agreed to us getting in touch with you.

Most people think that Asthma only affects children - but in fact it can affect adults as well. Recently, a new breathing test has been developed, which shows us whether a person has any tendency towards having Asthma. This test is very safe, and is not painful or unpleasant, It is widely used in other hospitals, and has no lasting effects.

As part of our research study, we are going to measure exactly how common Asthma is in adults and older people, by using the new breathing test in groups of people both with and without Asthma. This is where you can help. All we are asking you to do is to fill in the questionnaire that is enclosed with this letter, and possibly to come to the new Clinical Physiology Department at the Manchester Royal Infirmary for a short visit. This would last for about 1-2 hours, and would involve a free medical checkup, a small blood sample, and perhaps the breathing test. All your

travel costs would be refunded - and if necessary we would arrange for a Taxi to bring you to and from the hospital.

At the end of the study, we should know a lot more about Asthma and the way it affects adults and older people. Taking part may not be of any immediate benefit to your own health, but with your permission we would inform your General Practitioner of the results of the breathing tests, if you had these performed. We hope that the results of this study will improve the treatment for other people with chest diseases in the future.

There is a prepaid envelope enclosed, so that you can send the completed questionnaire back to us. We hope to hear from you shortly. If you would like to know any more about the study, please feel free to contact us by post at Barnes Hospital, or by telephone at the Manchester Royal Infirmary.

With many thanks for your help,

Yours faithfully,

Dr. Deborah S. Renwick MRCP
(Clinical Lecturer in Medicine)

MANCHESTER CENTRAL HOSPITALS AND COMMUNITY CARE NHS TRUST

THE ROBERT BARNES MEDICAL UNIT

The Robert Barnes Medical Unit
Barnes Hospital
Kingsway, Cheadle SK8 2NY

Tel No :- 061 - 491 - 2300
Fax No :- 061 - 491 - 4479

Dear ,

We recently wrote to you about a Research Project based at the Manchester Royal Infirmary, and we sent you a Questionnaire to fill in. We are writing to you again because we have not yet had a reply from you.

We are studying breathing problems in adults and older people, but you can take part whether you have any breathing problems or not. There are two parts to the project:

1. A questionnaire about your general health, and whether you take any medicines or smoke cigarettes.
2. A visit to the Manchester Royal Infirmary (lasting 90 minutes), for a basic medical check-up, some breathing tests, and a small blood sample.

Not everyone who fills in a questionnaire would need to come for the hospital visit. If you did come, we would refund your travel expenses.

In case you have lost the questionnaire, we are sending another copy with this letter, as well as a postage paid envelope to send it back to us. Please could you also return the reply slip on the next page. Thankyou.

Yours sincerely,

REPLY SLIP

(PLEASE CROSS OUT THE PARTS WHICH DO NOT APPLY TO YOU)

I AM RETURNING THE COMPLETED QUESTIONNAIRE.....YES/NO

I AM WILLING TO COME FOR THE HOSPITAL VISIT IF REQUIRED
.....YES/NO

MANCHESTER CENTRAL HOSPITALS AND COMMUNITY CARE NHS TRUST

THE ROBERT BARNES MEDICAL UNIT

The Robert Barnes Medical Unit
Barnes Hospital
Kingsway, Cheadle SK8 2NY

Tel No :- 061 - 491 - 2300
Fax No :- 061 - 491 - 4479

Dear ,

Research Project on Asthma in Adults

We have written to you twice about this project, but have received no reply from you. We assume that you do not wish to be included in the project. However, it is very important for us to get some basic information about all of the people that we have written to. This is so that we can check that there is no difference between the people who have replied to our letters and the people who have not.

If the person to whom this letter is addressed no longer lives at your address, please return this letter to us so that we know the address is incorrect.

We would be grateful if you could answer the few simple questions on the next page, and send it back to us in the addressed envelope. All of the information we receive is completely confidential. If you send this information back to us, we will not need to contact you again about this project.

Thank you for your help.

Yours sincerely,

Name _____

How old are you? _____ years

Have you ever had ASTHMA?.....yes/no

Have you ever had BRONCHITIS?.....yes/no

Have you ever had HEART TROUBLE?.....yes/no

Have you had any other serious illnesses...yes/no

(if yes, what were they?_____

_____)

Do you smoke?.....yes/no

If not, are you an ex-smoker?.....yes/no

MANCHESTER CENTRAL HOSPITALS AND COMMUNITY CARE NHS TRUST

THE ROBERT BARNES MEDICAL UNIT

The Robert Barnes Medical Unit
Barnes Hospital
Kingsway, Cheadle SK8 2NY

Tel No :- 061 - 491 - 2300
Fax No :- 061 - 491 - 4479

Dear

RESEARCH PROJECT ON ASTHMA IN ADULTS

Thank you for returning the Questionnaire that we sent you a few weeks ago, and for agreeing to take further part in this Research Project. An appointment has been made for you to come to the Manchester Royal Infirmary for some breathing tests on

The appointment will last for approximately 90 minutes. IF YOU ARE NOT ABLE TO COME PLEASE LET US KNOW, BY TELEPHONING 276 8608 - we can then use the time for someone else.

Please come to the Department of Clinical Physiology. This is on the ground floor in Phase 2 of the Infirmary, which is the new part of the Hospital. I am enclosing a map to show you the way. If you are not sure how to get there, if you come to the new Main Entrance (off Nelson Street), there is a reception desk where you can get directions. We will refund your bus or taxi fares if necessary.

Dos and don'ts for the breathing tests:

1. DON'T keep the appointment if you have had a chest infection or "cold" within the last 6 weeks - please let us know, and we will delay your appointment to let your chest recover fully.
2. DON'T drink any tea, coffee or Coca-Cola for 12 hours before you come for the test - the caffeine interferes with the results!

DO feel free to eat or drink anything else!

3. If you use inhalers or "puffers" for your chest, please DON'T use them for 12 hours before you come for the test.
4. If you take any tablets or medicines for your chest (eg Ventolin/ Theophylline/ Phyllocontin/ Nuelin tablets) please

DON'T take these for the 24 hours before you come for the test.
Missing these tablets for one day is not dangerous in any way.
DO phone and ask us if you are not sure about your medicines.

Thank you again for taking part in this study. If you have any questions, please feel free to contact me at the Manchester Royal Infirmary.

Yours sincerely,

Dr Deborah S Renwick MRCP

APPENDIX 3: CONSENT FORM

BRONCHIAL RESPONSIVENESS AND ASTHMA STUDY - CONSENT FORM

AIMS OF STUDY

This is a research study to measure how common asthma is in adults and older people, and to try to improve the way in which we diagnose asthma in this age group.

WHAT IT INVOLVES

- 1.You will be asked to fill in a questionnaire about symptoms of asthma.
- 2.You may be asked to perform the new breathing test. This involves blowing into a special machine several times, to measure your breathing capacity. In between these measurements, you will be asked to inhale a medicine called Methacholine through a mouthpiece, for a few seconds at a time.
- 3.A blood sample will be taken.

SIDE EFFECTS

The breathing test has been used in adults (both young and old) and children, and is known to be safe. It produces a mild degree of airways wheeze, which is reversed at the end of the test. Most people do not experience any side effects - but a small number may notice some flushing of the face, or a mild headache for a short time. There are no lasting side effects.

CONSENT

I have read the information given above, and have had an opportunity to discuss it with one of the doctors involved. I agree to take part in this research study, and I understand that I am free to withdraw from it at any time.

Signature Date.....

Witness..... Name..... Date.....

MEDICAL CONFIRMATION

I confirm that I have explained the nature and purpose of this research project, and answered any questions fully.

Signature Name..... Date.....

APPENDIX 4: SUPPLEMENTARY QUESTIONNAIRE

6. Breathlessness

Do you feel breathless at any of the following times?

- in the morning
- at night
- after exercise
- when you have a chest infection or cold

Do any of the following make you feel breathless?

- cold air
- smoke
- traffic fumes
- perfume/hairspray

7. Cough

Do any of the following make you cough?

- cold air
- smoke
- traffic fumes
- perfume/hairspray

8. Sputum

Do you bring up sputum (spit/flem/phlegm) from your chest?

If yes, when does this happen? - mostly in the morning
mostly at night
at any time

Do you bring up sputum/spit/phlegm most days? (eg 4 days per week)

If yes, for how many months of the year do you bring up the sputum/spit/phlegm?

For how many years have you been bringing up sputum/phlegm?

NSBR PROJECT: SUPPLEMENTARY QUESTIONS

NAME.....

1.Passive smoking

- FOR NON-SMOKERS ONLY: Does anyone else in your household smoke?
- if yes, please give details
.....

2.Occupational exposure

As part of your job, have you ever been exposed to any of the following:

- asbestos
- chemical fumes
- smoke
- wood dust
- coal dust
- quartz
- aluminium production or processing
- soldering or welding

- if yes, please give details.....
.....

3.Airways Infection

Have you had an airways infection or chest cold in the last 6 weeks?

4.Menopause

FOR WOMEN ONLY: Do you still have monthly periods?

IF NOT: How long ago did they stop?

Are you taking Hormone Replacement Therapy (HRT)?

5.Wheeze/Chest tightness

Does your chest feel wheezy or tight at any of the following times?

- in the morning (for how long?...minutes/hours)
- at night
- after exercise
- when you have a chest infection or cold

Do any of the following things make your chest feel wheezy or tight?

- cold air
- smoke
- traffic fumes
- perfume/hairspray

APPENDIX 5: REPEAT CALIBRATION OF NEBULISERS

Nebuliser number	First repeat Mean output $\mu\text{l/sec}$ (Variability)	Second repeat Mean output $\mu\text{l/sec}$ (Variability)	Third repeat Mean output $\mu\text{l/sec}$ (Variability)
1	4.44 (4%)	3.92 (8%)*	3.89 (7%)*
2	4.02 (2%)	4.18 (4%)	4.07 (4%)
3	4.11 (3%)	3.68 (11%)*	4.05 (6%)*
4	4.52 (8%)*	3.92 (10%)*	4.20 (4%)
5	3.65 (6%)*	4.03 (4%)	4.08 (5%)
6	4.27 (6%)*	4.01 (5%)	3.91 (8%)
7	4.07 (4%)	4.04 (1%)	4.07 (2%)
8	4.85 (5%)	4.25 (5%)	3.99 (7%)*
9	4.42 (7%)*	4.12 (5%)	4.11 (3%)
10	4.39 (4%)	3.80 (9%)*	3.92 (8%)*
11	3.56 (8%)*	4.01 (5%)	4.51 (3%)
12	4.08 (5%)	4.01 (5%)	4.51 (3%)

*denotes nebulisers discarded and replaced

APPENDIX 6: RESULTS OF REPEATED BRONCHIAL CHALLENGE IN 40
SUBJECTS

Age	PD ₂₀ (FEV ₁) day 1*	PD ₂₀ (FEV ₁) day 2	DRS(FEV ₁) day 1**	DRS(FEV ₁) day 2
29	80	75	239	249
24	-	-	2.62	3.71
25	7.50	5.00	2169	4030
25	170	110	112	192
27	-	-	1.39	0.78
26	-	-	1.39	1.30
24	-	-	2.56	2.74
25	6000	3500	3.53	7.08
26	5000	-	3.41	2.02
33	7.00	6.00	2557	3257
24	-	6400	1.85	3.30
28	-	6400	1.55	2.98
24	2500	-	6.59	3.77
35	-	-	0.17	0.34
28	-	-	0.31	0.78
26	-	-	2.48	2.92
29	-	-	3.13	2.23
26	-	-	2.58	2.98
31	6.00	6.00	3095	3289
63	180	270	110	64.9
71	-	6400	2.37	3.02
66	120	120	167	112
76	170	230	117	86.6
73	160	250	245	103
70	2800	1580	10.61	25.7
67	100	100	247	186

Age	PD ₂₀ (FEV ₁) day 1	PD ₂₀ (FEV ₁) day 2	DRS(FEV ₁) day 1	DRS(FEV ₁) day 2
57	12.5	11	1084	1670
74	1100	1700	15.4	11.8
58	46	30	440	604
66	2340	-	34.7	10.2
70	440	1100	34.0	14.2
74	-	-	2.24	2.59
64	-	2000	3.94	7.46
70	-	4000	1.26	3.58
61	56.0	46.0	333	418
84	2.30	1.30	9406	17080
75	12.0	25.0	1810	778
64	3.20	6.00	4554	3397
77	3200	280016.18	6.5	

* μg methacholine

** %fall FEV₁/ μg methacholine

APPENDIX 7: PUBLISHED PAPERS

In conclusion, the airway response to SO₂ involves the release of inflammatory mediators. In addition, the parasympathetic reflexes which play a part in the SO₂-induced bronchoconstriction have the potential to be modulated by opioids.

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Prevalence and treatment of chronic airways obstruction in adults over the age of 45

Deborah S Renwick, Martin J Connolly

Abstract

Background - Chronic airways obstruction is common in adults and the elderly. To investigate the possibility that older adults with obstructive airways disease frequently do not receive appropriate treatment, the respiratory symptoms, medication use, and pulmonary function were studied in a random sample of white adults aged over 45 living in central Manchester, UK.

Methods - A postal questionnaire survey was performed on 783 men and women aged 45 years and over selected from GP lists by random number tables. Subjects completing the questionnaire were invited to attend for pulmonary function testing and methacholine challenge (Newcastle dosimeter method).

Results - The questionnaire response rate was 92.3% (723 subjects). The mean age of the population was 66.1 years and 57.2% were women; 29.2% were current smokers and 37.3% were ex-smokers. Asthma or bronchitis was reported by 30.0%. Two hundred and forty seven representative subjects attended for pulmonary function testing and spirometric evidence of chronic airways obstruction was found in 26.4%. Respiratory symptoms were reported by 76.6% of subjects with chronic airways obstruction; 55.0% had features which may predict potential improvement on treatment (increased non-specific bronchial responsiveness or significant bronchodilator reversibility). However, only 55.4% of subjects with airways obstruction had received a diagnosis of asthma or chronic bronchitis and only 36.9% were using inhaled bronchodilators or steroids.

Conclusions - Chronic airways obstruction is very common in adults in this inner city population, but is frequently overlooked. Most subjects with chronic airways obstruction are not receiving appropriate treatment.

(Thorax 1996;51:164-168)

Keywords: chronic airways obstruction, inhaled bronchodilators, epidemiology.

Chronic airways obstruction is common; surveys give a prevalence in the elderly of approximately 16% (asthma plus smoking-related airways obstruction).^{1,2} However, studies often contain few elderly people.^{3,4}

It was our clinical impression that many older people with chronic airways obstruction do not

receive appropriate drug treatment. In a study of older adults attending day hospitals and living in local authority homes, Banerjee *et al* found a prevalence of reversible airways obstruction of >40%, although only 3% were using respiratory medications.⁵ Two surveys of elderly nursing home residents found that 10% or less were prescribed bronchodilators^{6,7}; this is probably much less than the proportion with chronic airways obstruction given the estimate for the general elderly population.² There have been no assessments of the proportion of people with chronic airways obstruction receiving appropriate drug treatment among the community dwelling elderly. We have investigated respiratory symptoms, medication use, and pulmonary function in an age stratified random population sample of adults over the age of 45.

Methods

POPULATION SAMPLING

The study was approved by Central Manchester Health Authority ethical committee. We aimed to study a random sample of the local population aged ≥ 45 years including large numbers of elderly people. Between January 1992 and February 1994 names and addresses were taken using random number tables from practice lists of 22 local general practitioners. Non-white subjects were excluded because of interracial differences in bronchial responsiveness.⁸ General practitioners excluded those who were confused or house-bound, plus the few unsuitable for other reasons. In order to increase the numbers of older subjects only those aged ≥ 70 were selected during the final months of recruitment.

Subjects were sent an explanatory letter and questionnaire concerning previous diagnoses of asthma, chronic bronchitis, and ischaemic heart disease; current medication; smoking history; and respiratory symptoms. Questions on respiratory symptoms were adapted from the MRC respiratory symptoms questionnaire.⁹ Non-responders were sent a repeat questionnaire, followed if necessary by an abbreviated questionnaire containing only questions about previous diagnoses and smoking habits. Half of the persistent non-responders were randomly contacted by telephone or home visit.

PULMONARY FUNCTION TESTING

Patients were excluded from the methacholine challenge if they had a history of ischaemic heart disease or were receiving current medication with β blockers, anticholinergic med-

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ications, or oral steroids. Subjects not excluded on these grounds were invited to attend Manchester Royal Infirmary. Attendance was delayed for six weeks after respiratory tract infection or exacerbation of wheezing. Subjects were requested to refrain from caffeine for 12 hours, and to omit bronchodilators for 12 hours (inhalers), 24 hours (oral preparations), or 48 hours (sustained release preparations) before attendance.

Written informed consent was obtained from all subjects. Resting 12-lead electrocardiography (ECG) was performed, and if this showed evidence of myocardial ischaemia subjects were also excluded from methacholine challenge. Baseline pulmonary function was measured (Compact, Vitalograph, Buckingham, UK) (mean of the best six readings reproducible within 10%).^{10 11} Methacholine challenge was performed by subjects with baseline forced expiratory volume in one second (FEV₁) of $\geq 60\%$ predicted¹²; if FEV₁ was $<60\%$ predicted β agonist reversibility was assessed.

β AGONIST REVERSIBILITY

FEV₁ measurements were repeated 10 minutes after inhalation of 1 mg terbutaline via a metered dose inhaler and large volume spacer (Nebuhaler, Astra Pharmaceuticals, Hertfordshire, UK). A positive result was defined as an increase in FEV₁ of ≥ 160 ml.¹³

METHACHOLINE CHALLENGE

This was performed by the Newcastle dosimeter method.^{10 11 14} Briefly, doubling doses of nebulised methacholine were inhaled at five minute intervals by the subject while seated and wearing a noseclip. FEV₁ (mean of three recordings reproducible within 10%) was measured before each subsequent dose. End points were a 20% decrease in FEV₁ or administration of a maximum cumulative dose of 6.4 mg methacholine. Results were expressed as the methacholine dose producing a 20% fall in FEV₁ (PD₂₀).¹¹ Increased non-specific bronchial responsiveness was defined as a PD₂₀ of <400 μ g methacholine.¹¹ Repeatability of methacholine challenge was assessed in 21 subjects who agreed to attend on a second occasion 3–10 days after the initial challenge.

DATA ANALYSIS

Subgroups were compared by grouped *t* test and χ^2 tables. Significance was defined at the 5% level.

Results

DEMOGRAPHIC DETAILS OF STUDY POPULATION AND RESPONSE RATE

Of 893 subjects contacted, 110 were ineligible (78 incorrect address, 15 dead, six non-white, 11 housebound/confused/disabled). This left 783 eligible subjects, 508 of whom returned the full questionnaire and 170 the abbreviated questionnaire. Twenty nine subjects declined

Table 1 Demographic details of study population

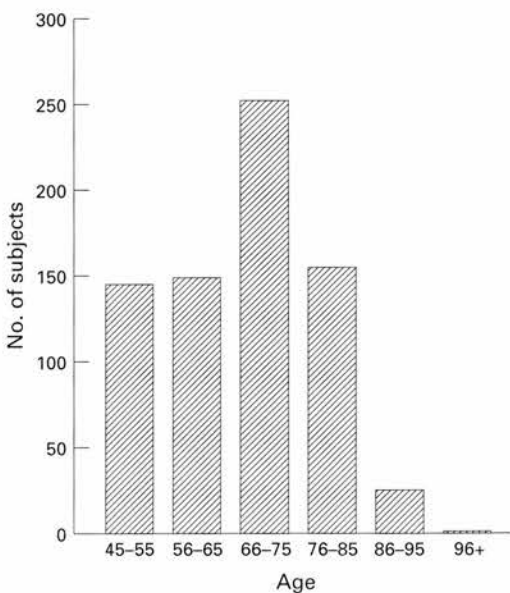
Mean age (years)	66.1
% women	57.2
% reporting asthma	7.3
% reporting bronchitis	15.4
% reporting asthma plus bronchitis	7.3
% current smokers	29.2
% ex-smokers	37.3

to take part. Forty five randomly selected non-responders agreed to complete the abbreviated questionnaire; a further 12 were found to have moved away before the start of the study and were therefore not included. Thus, questionnaire information was available for 723 (92.3%) of the 783 eligible subjects. The age and sex of all subjects was obtained from GP records. Demographic details of the study population are summarised in table 1; the age distribution of the population is shown in the figure.

Fifty three subjects reported asthma, 111 bronchitis, and a further 53 both asthma and bronchitis; overall, 217 of the 723 (30.0%) reported asthma or bronchitis. This proportion was not significantly different in subjects aged less than 65 years (94 of 292 subjects (32.2%)) or 65 years and over (123 of 431 subjects (28.5%)). Of the 508 subjects returning the full questionnaire 15% were using inhaled medications. The prevalence of inhaler use by subjects reporting asthma or bronchitis was 46.4% (72.0% for subjects reporting asthma, 39.9% for those reporting bronchitis).

PULMONARY FUNCTION, REVERSIBILITY AND METHACHOLINE CHALLENGE

Of the 508 subjects returning the full questionnaire, the responses of 113 excluded them from methacholine challenge (ischaemic heart disease 83; β blockers/anticholinergics/oral steroids 48). The remaining 395 were invited to attend for methacholine challenge: 247 subjects actually attended (62.5% of those invited to attend; 31.5% of the total eligible study popu-



Age distribution of responders to questionnaire.

Table 2 Mean (SD) results of spirometric tests

	All attenders (n = 246)	Subjects with chronic airways obstruction (n = 65)	Subjects without chronic airways obstruction (n = 181)
FEV ₁ /FVC%	69.2 (11.6)	54.2 (7.7)	74.6 (7.2)
FEV ₁ (% predicted)	86.9 (24.5)	63.6 (24.0)	94.6 (18.9)
Age (years)	64.5 (10.8)	66.3 (10.0)	63.8 (11.1)
% women	56.7	53.8	57.4

FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity

lation). The mean age of attenders was 64.5 years (range 45–86 years); this was younger than the population as a whole ($p = 0.02$, grouped t test). There was no significant difference between the 247 attenders and the 783 eligible subjects in sex distribution (56.7% women in attender group), reporting of asthma or bronchitis, reporting of respiratory symptoms, or smoking habits (33.6% of attenders were current smokers and 38.5% were ex-smokers).

One subject was unable to perform reproducible measurements of baseline spirometry and thus data were available for 246 attenders (table 2). Chronic airways obstruction was defined as an FEV₁/FVC% of <65% for subjects aged <65 years; for those aged ≥ 65 years a predicted value and lower limit of normal for FEV₁/FVC% was calculated as described by Enright *et al.*¹⁵ Using these criteria, the prevalence of chronic airways obstruction was 26.4% (22.9% in 118 attenders aged <65 years and 29.7% in the 128 attenders aged ≥ 65 ($\chi^2 = 1.46$, $p = 0.2$)). Airways obstruction was equally common in men and women, but more common in current (39.7%) and ex-smokers (27.7%) than in those who had never smoked (12.8%; $\chi^2 = 14.1$, $p = 0.001$).

In 22 subjects with chronic airways obstruction baseline FEV₁ was <60% predicted, and thus β agonist reversibility was measured. Ten of these subjects (45.5%) had ≥ 160 ml improvement in FEV₁ following terbutaline. Of the remaining 43 subjects with chronic airways obstruction five were unable or unwilling to complete the methacholine challenge. Non-specific bronchial responsiveness was increased in 23. Thus, overall 33 of 60 (55.0%) subjects with chronic airways obstruction had either increased non-specific bronchial responsiveness or significant β agonist reversibility. In 21 subjects attending twice, PD₂₀ measurements were repeatable within two doubling doses of methacholine.

For the whole attender group multiple regression analysis with log PD₂₀ as the dependent

Table 4 Proportion of subjects receiving inhaled β agonists or steroids

	Chronic airways obstruction (n = 65)	No chronic airways obstruction (n = 181)
No treatment	41 (63.1%)	169 (93.4%)
β agonist only	9 (13.8%)	4 (2.2%)
Steroid \pm β agonist	14 (21.5%)	8 (4.4%)

variable and age, sex, smoking habit, and baseline FEV₁ (% predicted) as independent variables showed a significant positive relationship between log PD₂₀ and baseline FEV₁ ($p = 0.0001$; $R = 0.3$), but no relationship between log PD₂₀ and the other independent variables.

RESPIRATORY SYMPTOMS AND USE OF BRONCHODILATORS

Subjects with chronic airways obstruction reported significantly more respiratory symptoms than those without, and wheeze was the commonest symptom (table 3); 76% of subjects with airways obstruction reported one or more symptoms. However, as symptoms were also common in those without chronic airways obstruction, the positive predictive value of symptoms for "obstructive" pulmonary function test results was low: only 35.8% of symptomatic subjects had chronic airways obstruction on pulmonary function testing. The symptom with the highest positive predictive value for airways obstruction was breathlessness (MRC grade 3+)⁹: 19 (42.2%) of the 45 subjects reporting breathlessness had evidence of airways obstruction. Combinations of two or more symptoms were reported less frequently, but were more commonly associated with airways disease. For example, only 21 patients reported cough plus wheeze plus breathlessness, but 14 of them had airways obstruction (positive predictive value 66.7%).

Asthma or bronchitis was reported by 55.4% of subjects with airways obstruction and 23.7% of those with "normal" FEV₁/FVC ($\chi^2 = 21.9$, $p < 0.001$). The positive predictive value of reported asthma or bronchitis for evidence of chronic airways obstruction on pulmonary function testing was 45.6%.

Twenty three (35.4%) of the 65 subjects with chronic airways obstruction were using inhaled treatment (table 4), most commonly both inhaled steroids and β agonists. Only two subjects were taking oral β agonists and none theophylline. Age did not significantly affect the likelihood of treatment: eight of 27 (20.6%) subjects of <65 years and 15 of 38 (39.5%) of ≥ 65 years were using treatment. Treated subjects had significantly worse baseline airways obstruction (mean (SE) FEV₁/FVC% = 48.6 (1.8)%) than those on no treatment (57.5 (0.7)%; $t = 5.3$, $p < 0.0001$). Respiratory symptoms were reported by 70.0% of untreated subjects with chronic airways obstruction.

Discussion

Our data confirm the high prevalence of chronic airways obstruction in white adults in central

Table 3 Number (%) of symptoms reported

	Subjects with chronic airways obstruction (n = 65)	Subjects without chronic airways obstruction (n = 181)	χ^2 (p value)
Cough (%)	33 (50.8)	50 (27.6)	10.7 (0.001)
Sputum (%)	36 (55.4)	53 (29.3)	14.4 (<0.001)
Wheeze (%)	39 (60.0)	55 (30.4)	17.0 (<0.001)
Breathlessness† (%)	19 (29.2)	26 (14.4)	7.0 (<0.01)
One or more symptoms (%)	49 (76.6)	88 (50.0)	13.5 (<0.001)

† Breathless when walking on the level or at rest (equivalent to MRC grade 3+).⁹

Manchester. However, it is relevant to ask whether our study sample is representative. Many subjects initially selected had died or left the area. This problem has been described in other studies using information from GP lists and seems unavoidable.¹⁶ Nonetheless, the high response rate (>90%) makes it likely that our figures are accurate. The preponderance of women in our population is expected in a sample containing many elderly people and agrees with OPCS estimates for central Manchester (53% women in the population aged >45).¹⁷ Our figures for current and ex-smoking were higher than recent OPCS estimates (29% current smokers in a population aged >50 years).¹⁸ It is probable that our results represent the situation in other urban white populations in Britain.

Unfortunately, only 31.5% of the eligible population attended for methacholine challenge. Although 113 subjects were excluded because of ischaemic heart disease or medications, most non-attenders were simply not prepared to undergo tests. This was particularly true of older subjects, and so attenders were younger than non-attenders. Similar problems have been reported in other studies of bronchial responsiveness.^{2,19,20} Nonetheless, attenders were representative of the study population in terms of sex distribution, smoking, diagnosed asthma/bronchitis, and reported respiratory symptoms.

Other studies of adults aged ≥ 65 years have found a lower prevalence of airways obstruction. In a postal survey 8.4% reported asthma and 16.4% chronic bronchitis¹; chronic airways obstruction has been found in 6.9% ($FEV_1/FVC < 65\%$)²¹ and 15.6% ($FEV_1/FVC < 60\%$) in population studies.² This variation may reflect differences in smoking habits or environmental influences between populations.

The proportion of subjects with diagnosed asthma or chronic bronchitis prescribed inhaled medications has been assessed in a study in the northern region of England using computerised GP records.²² In that study inhalers were prescribed for 6% of patients with chronic bronchitis and 66% of those with asthma (38% of patients with a recorded diagnosis); prescribing rates were higher for patients aged 65–74. Our figures for prescribing in central Manchester are higher, perhaps because of differences in the population age range, data source, and diagnostic practices.

The problems of self-reported diagnoses as a measure of asthma prevalence have been discussed.²³ The lack of agreed diagnostic criteria for asthma and chronic airways obstruction means that physicians vary in their diagnostic labelling and may be influenced by non-clinical parameters such as age and sex.²⁴ As a result, patients may acquire multiple diagnoses²⁵; this is demonstrated by the number of subjects in our population reporting both asthma and bronchitis. Some studies have found evidence of overreporting of unconfirmed diagnoses^{3,26}; others have suggested underreporting, particularly by older men with chronic bronchitis.²⁷

We have objectively assessed the prevalence of chronic airways obstruction by spirometric testing in a representative sample. Since $FEV_1/FVC\%$ decreases with age, we calculated predicted levels and lower limits of normal for subjects aged ≥ 65 years.¹⁵ To avoid overestimation of airways reversibility in patients with low baseline FEV_1 we defined reversibility as a fixed volume increase in FEV_1 , rather than a percentage increase over baseline.¹³ Measurement of bronchial responsiveness by the New-castle dosimeter method usually includes six measurements of FEV_1 after each methacholine dose.¹¹ To avoid fatigue in our elderly population this was reduced to three; this adapted method has been shown to be reproducible in older adults.¹⁰ As is customary for this method of bronchial challenge, PD_{20} was calculated using the mean rather than the maximum of the three FEV_1 recordings^{10,11}; we confirmed that this gave better repeatability.

The prevalence of reported asthma or bronchitis was similar to that of measured chronic airways obstruction. However, both reported diagnoses and symptoms were poor predictors of chronic airways obstruction. This has implications for other epidemiological studies of asthma or chronic airways obstruction, some of which have relied solely on self-reporting of diagnoses and symptoms.^{28,29}

Only one third of subjects with airways obstruction were using inhaled medications. This may reflect tolerance of respiratory symptoms by elderly people or therapeutic nihilism on behalf of their doctors. The lack of patients taking theophylline is surprising; this may reflect either poor patient compliance or local prescribing habits. The need for serum monitoring and the incidence of side effects has decreased the popularity of theophylline.³⁰

Over half of our subjects with chronic airways obstruction had bronchodilator reversibility or increased bronchial responsiveness. The latter has been shown to predict spirometric improvement on treatment in elderly asthmatic subjects.¹⁰ A single measurement of bronchodilator reversibility is less reliable as a predictor of response to treatment.³¹ The significance of increased bronchial responsiveness in patients with chronic airways obstruction is also unclear; a strong correlation between baseline FEV_1 and PD_{20} in these patients has led to the suggestion that increased bronchial responsiveness is merely the result of reduced airway calibre rather than an indication of airways lability.^{32,33} We have confirmed the relationship between baseline FEV_1 and PD_{20} , but the low coefficient of multiple regression suggests that the high prevalence of increased bronchial responsiveness in our subjects is not merely the result of low FEV_1 .

In summary, we have found high levels of untreated chronic respiratory morbidity in the adult white population of central Manchester, but no evidence of age bias in the proportion of patients receiving treatment. Adults with respiratory symptoms should have pulmonary function formally assessed; those with airways obstruction may benefit from bronchodilator treatment.

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increase in renal blood flow in these animals. However, other studies have found no change in systemic arterial pressure during infusions of L-arginine.¹⁷ In our study we have shown that the increase in renal blood flow seen with infusions of L-arginine in humans is independent of changes in systemic blood flow. This suggests that L-arginine acts on the renal vasculature to produce vasodilatation. This may be due to an increase in NO production.

In the group of patients with hypoxic COPD L-arginine had no effect on renal blood flow. Defective endothelial function has been demonstrated in forearm arteries in patients with heart failure secondary to ischaemic heart disease,²⁷ and our results suggest that defective endothelial function is present in the renal vessels of patients with cor pulmonale. This is in contrast to patients with congestive heart failure secondary to ischaemic heart failure whose renal blood flow is relatively preserved.²⁸

In a previous study we have shown that oxygen is a potent renal vasodilator in hypoxic patients with COPD.^{6,7} A possible mechanism of this effect is that oxygen, which is necessary for the production of nitric oxide, is deficient in the endothelium of these patients and therefore NO dependent vasodilator tone is reduced causing vasoconstriction. Alternatively, oxygen concentrations might be necessary at a high level to synthesise nitric oxide by a different mechanism (an example might be by influencing the availability of ATP). Finally, this effect of oxygen might be via a different mechanism. These hypotheses might be addressed by assessing renal blood flow with and without oxygen therapy in the presence and absence of infused L-arginine. However, in this study we have shown a disturbance in the L-arginine/nitric oxide pathway in hypoxic patients with COPD. This is evidence that the derangement in renovascular control in patients with COPD and cor pulmonale, and the renal vasodilatation seen with oxygen therapy in these patients, may be caused, at least in part, by an abnormality of the nitric oxide pathway. Further work, as outlined above, will be needed to clarify this.

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Impact of obstructive airways disease on quality of life in older adults

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Abstract

Background – Obstructive airways disease adversely affects quality of life, although relationships between quality of life and lung function have been shown to be weak. The relationships between the results of a quality of life questionnaire, spirometric tests, and methacholine bronchial challenge were investigated in a population sample of middle aged and elderly people.

Methods – A random population sample of the white population of Central Manchester, UK were contacted by post. Respondents were invited to undergo bronchial challenge with methacholine (Newcastle dosimeter method) and to complete the St George's Respiratory Questionnaire. This self-completed questionnaire quantifies quality of life as three component scores, with higher scores indicating greater impairment of quality of life.

Results – Two hundred and twenty seven subjects aged 45–86 years completed the St George's Questionnaire and performed spirometric tests; 190 completed the methacholine challenge. All quality of life scores were higher in subjects with a forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) of <65%, indicating impaired quality of life in subjects with airways obstruction. There was no relationship between quality of life and age. Multiple regression analysis showed independent relationships between quality of life scores and both baseline FEV₁ and bronchial responsiveness. However, the amount of variation in quality of life attributable to variation in FEV₁ or bronchial responsiveness was less than 10%. Subgroup analysis indicated that the quality of life score was independently associated with bronchial responsiveness and not FEV₁ in subjects aged <65 years, but with baseline FEV₁ and not bronchial responsiveness in older subjects.

Conclusions – Obstructive airways disease significantly impairs quality of life in adults. The reduction in quality of life in these patients is related to both baseline pulmonary function and non-specific bronchial responsiveness. The impact of airways obstruction on quality of life does not decrease with advancing age.

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Obstructive airways disease is common in the elderly, affecting approximately 16% of people over the age of 65.¹ It has a substantial impact on quality of life, impairing not only physical, but also psychological and social function.^{2,3} The relationship between the degree of quality of life impairment and the severity of airways obstruction as measured by pulmonary function tests has, however, generally been found to be weak.^{2–5}

It has been suggested that the impact of obstructive airways disease on quality of life may be less in older subjects.^{3,5,6} We have therefore compared the quality of life in subjects with and without chronic airways obstruction and bronchial hyperresponsiveness to assess the effects of chronic obstructive airways disease and asthma on quality of life in a population sample of adults aged 45–86 years.

Methods

Names of adults aged ≥45 were taken using random number tables from practice lists of 22 local general practitioners. Those who were confused or housebound were excluded, together with the few unsuitable for other reasons. Non-white subjects were excluded because of interracial differences in bronchial responsiveness.⁷

Subjects were sent an explanatory letter and questionnaire concerning previous asthma, bronchitis, ischaemic heart disease, smoking history, and current medication. Non-responders were sent a reminder, followed by a second reminder with an abbreviated questionnaire. A random sample of persistent non-responders was contacted by telephone or home visit.

Questionnaire responses were used to identify those excluded from methacholine challenge. Exclusion criteria were ischaemic heart disease or medication with β blockers, anticholinergics or oral steroids. Subjects not excluded on this basis were invited to attend. Attendance was delayed for six weeks after a respiratory tract infection or exacerbation of wheezing. Subjects were requested to refrain from caffeine for 12 hours and to omit bronchodilators for 12 hours (inhalers), 24 hours (oral preparations), or 48 hours (sustained release preparations) before attendance.

Written informed consent was obtained from all subjects attending and the study was approved by the Central Manchester Health Authority ethical committee. A resting 12 lead electrocardiograph was performed, and subjects with evidence of myocardial ischaemia were excluded from methacholine challenge.

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Baseline pulmonary function was measured (Compact, Vitalograph, Buckingham, UK) using the mean of six reproducible readings. Methacholine challenge was performed only if baseline forced expiratory volume in one second (FEV₁) was $\geq 60\%$ predicted.

Subjects completed the St George's Respiratory Questionnaire,⁸ which is a self-completed questionnaire validated as a measure of quality of life in subjects with chronic airways obstruction. Three component scores are calculated: Symptoms (frequency and severity), Activities (causing or limited by breathlessness), and Impacts (on employment and emotions, feelings of panic or control), as well as a total score. Higher scores indicate greater morbidity.

Methacholine challenge was performed by the Newcastle dosimeter method.^{9,10} Briefly, doubling doses of nebulised methacholine were inhaled at five minute intervals by the subject while seated and wearing a noseclip. FEV₁ was measured before each subsequent dose; as recommended, three readings reproducible within 10% were performed each time and the mean was used. End points were a 20% decrease in FEV₁ or administration of a maximum cumulative dose of 6.4 mg methacholine. Results were expressed as (a) dose of methacholine producing a 20% fall from baseline FEV₁ (PD₂₀), and (b) the slope of the dose-response curve to methacholine (dose-response slope) which gives a continuous non-censored measure of bronchial responsiveness expressed in units of percentage decline in FEV₁ per μg methacholine.¹¹

DATA ANALYSIS

St George's Questionnaire scores and values for the dose-response slope were log transformed to achieve normal distribution. To allow log transformation of all St George's Questionnaire scores, the value 0.5 was allocated to those subjects with scores of 0. One subject had a slight increase in FEV₁ during methacholine challenge producing a negative dose-response slope; to allow logarithmic conversion of this result a constant of 0.43 was added to all dose-response slope values.¹² Relationships between quality of life scores and pulmonary function were analysed by linear correlation and multiple regression. Subgroups were compared by grouped *t* tests.

To avoid the age and height bias associated with the expression of FEV₁ as a percentage of predicted values, baseline FEV₁ was expressed as standardised residuals (SR) for calculation of correlation coefficients and multiple regression.¹³ These were calculated using the equation $SR = (\text{recorded value} - \text{predicted value}) / \text{RSD}$, where RSD is the residual standard deviation about the regression equation used to calculate the predicted values.¹⁴ The prediction equations used for the calculation of standardised residuals were derived from urban white UK adults over a wide age range comparable to that of the current study.¹⁵

Chronic airways obstruction was defined as a ratio of FEV₁ to forced vital capacity (FVC)

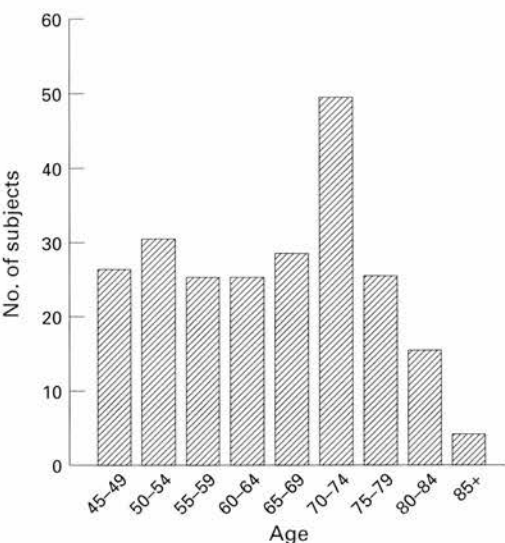


Figure 1 Age distribution of subjects performing spirometric tests.

of $<65\%$ in those aged <65 years; since this ratio decreases with normal ageing, a predicted value and lower limit of normal for FEV₁/FVC was calculated for subjects aged ≥ 65 using equations from the Cardiovascular Health Study.¹⁶

Bronchial hyperresponsiveness was defined as a PD₂₀ of $\leq 100 \mu\text{g}$ methacholine; this level has been shown to have a predictive value for current asthma of nearly 100%.¹⁷ In all cases significance was defined at the 5% level.

Results

We contacted 783 eligible subjects; 508 returned the full questionnaire and could be assessed for suitability for methacholine challenge. A further 215 subjects completed abbreviated questionnaires (overall response rate 92.3%). Responders were representative of the population in age and sex distribution; those completing full and abbreviated questionnaires were similar in terms of smoking history and prevalence of diagnosed asthma or bronchitis.

One hundred and thirteen subjects were excluded from methacholine challenge because of heart disease or medication; of the 395 invited to attend, 247 agreed. There was a slight age difference between attenders and non-attenders (mean age of attenders 64.5 years, non-attenders 66.1; $p=0.02$), but attenders were representative in terms of smoking habit, diagnosed asthma and bronchitis, and prevalence of respiratory symptoms.

Two hundred and twenty seven attenders performed reproducible spirometric tests and completed the St George's Questionnaire, of whom 26 had a baseline FEV₁ of $<60\%$ predicted, two had electrocardiographic evidence of ischaemic heart disease, and nine were unable to complete the methacholine challenge. Challenge results were thus available for 190 subjects.

One hundred and twenty eight of the 227 subjects who performed spirometric tests were women. The age distribution is shown in fig 1.

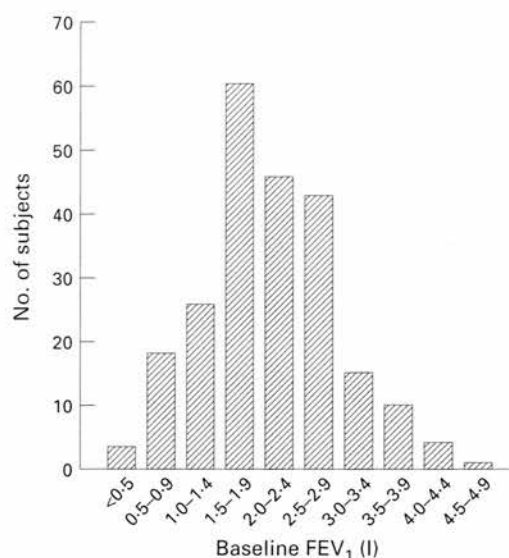


Figure 2 Distribution of baseline forced expiratory volume in one second (FEV_1).

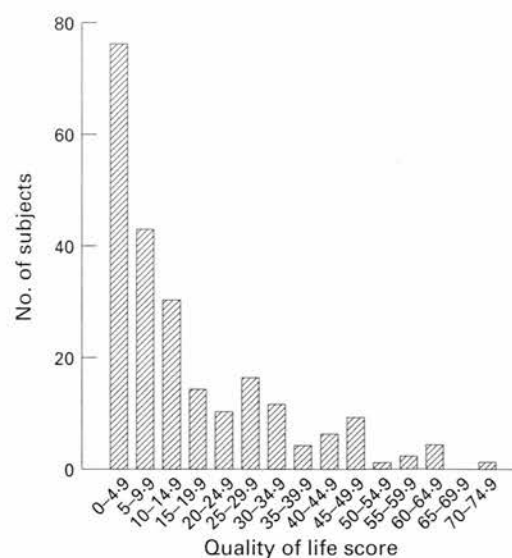


Figure 3 Distribution of total quality of life scores.

Seventy one subjects were current smokers and 91 were ex-smokers. Thirty three reported a previous diagnosis of asthma and 52 "bronchitis"; 33 were using inhaled bronchodilators and/or an inhaled steroid.

Figure 2 shows the distribution of baseline FEV_1 . Fifty nine subjects had chronic airways obstruction (FEV_1/FVC of $<65\%$ or lower than predicted level)¹⁶; the mean (SD) age of these subjects was 66.2 (10.0) years (range 47–84). There was no age difference between these subjects and the 168 subjects without airways obstruction (mean (SD) age 64.1 (11.2) years, range 45–86; $t = -1.3$, $p = NS$). Twenty five subjects with chronic airways obstruction were aged <65 years and 34 were aged ≥ 65 years ($\chi^2 = 0.6$, $p = NS$).

A PD_{20} value was obtained in 135 subjects of whom 48 had bronchial hyperresponsiveness ($PD_{20} \leq 100 \mu g$). The mean ages of subjects with and without bronchial hyperresponsiveness were similar ($PD_{20} \leq 100 \mu g$: mean (SD) age 64.4 (11.2), range 45–86; $PD_{20} > 100 \mu g$: mean (SD) age 63.6 (10.8), range 45–86; $t = -0.4$, $p = NS$). Twenty three subjects with bronchial hyperresponsiveness were aged <65 years and 25 were ≥ 65 years ($\chi^2 = 0.1$, $p = NS$).

The distribution of total St George's Questionnaire scores is shown in fig 3; 16 subjects had a score of zero (indicating no quality of life impairment). Geometric mean quality of

life scores were similar for men and women. There was no correlation between quality of life scores and age. However, the mean Activities score was significantly higher for subjects aged ≥ 65 years (geometric mean (SD) 1.04 (0.71)) than for those aged <65 years (0.81 (0.76); $t = -2.34$, $p = 0.02$).

Total quality of life scores were significantly higher in the 59 subjects with chronic airways obstruction, indicating quality of life impairment in subjects with obstructive airways disease. Similarly, all quality of life scores except the Impacts score were significantly higher in those with bronchial hyperresponsiveness (table 1).

For the whole group there was significant negative correlation between log total quality of life score and baseline FEV_1 (expressed as standardised residuals) ($r = -0.47$, $p < 0.001$; fig 4). There was also a significant positive correlation between log total quality of life score and log dose-response slope ($r = 0.20$, $p < 0.005$; fig 5). Similar correlations were seen between baseline FEV_1 (standardised residuals) and log Activities score ($r = -0.38$, $p < 0.001$), log Impacts score ($r = -0.47$, $p < 0.001$) and log Symptoms score ($r = -0.37$, $p < 0.001$), and between the log dose-response slope and log Activities score ($r = 0.18$, $p < 0.01$), log Impacts score ($r = 0.17$, $p < 0.01$), and log Symptoms score ($r = 0.23$, $p = 0.001$).

Table 1 Geometric mean (SD) quality of life scores in subjects with and without chronic airways obstruction and bronchial hyperresponsiveness

	Total score	Activities score	Impacts score	Symptoms score
Subjects with chronic airways obstruction	1.18 (0.49)	1.18 (0.65)	0.76 (0.73)	1.41 (0.56)
Subjects without chronic airways obstruction	0.84 (0.53)	0.85 (0.75)	0.34 (0.69)	0.92 (0.77)
	$t = -4.2$ $p < 0.0001$	$t = -3.0$ $p < 0.005$	$t = -3.9$ $p < 0.0001$	$t = -4.5$ $p < 0.0001$
Subjects with bronchial hyperresponsiveness	0.98 (0.47)	1.03 (0.64)	0.39 (0.70)	1.21 (0.70)
Subjects without bronchial hyperresponsiveness	0.81 (0.51)	0.80 (0.73)	0.29 (0.70)	0.89 (0.74)
	$t = -2.0$ $p = 0.05$	$t = -1.9$ $p = 0.05$	$t = -0.9$ $p = NS$	$t = -2.6$ $p = 0.01$

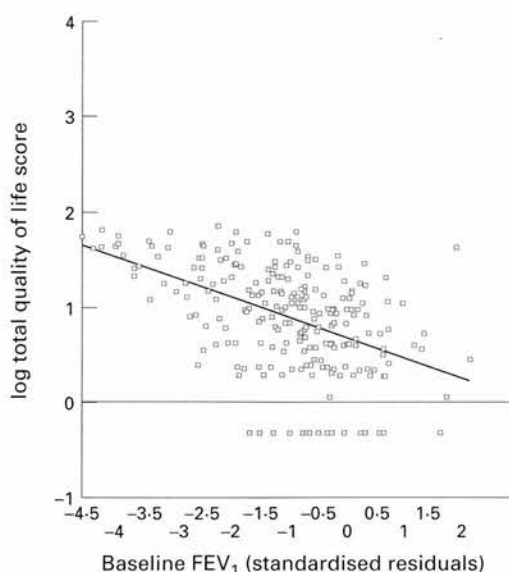


Figure 4 Relationship between total quality of life score and baseline FEV₁ (standardised residuals).

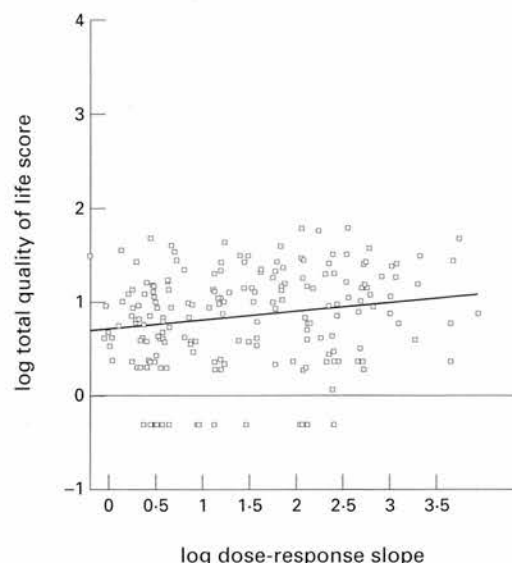


Figure 5 Relationship between total quality of life score and log dose-response slope.

Multiple regression analysis was performed with quality of life score as the dependent variable and baseline FEV₁, log dose-response slope, age, and sex as independent variables. As there was a significant correlation between the baseline FEV₁ and log dose-response slope, an interaction term was included in the regression¹²; this was not significantly related to quality of life in any of the analyses. For the whole subject group, both total and separate component quality of life scores showed independent negative relationships with baseline FEV₁ (standardised residuals); only the Symptoms score showed a significant association with the log dose-response slope (table 2).

The effect of smoking on quality of life was assessed by comparing total St George's Ques-

tionnaire scores of never smokers and smokers (ex-smokers plus current smokers). Quality of life was significantly impaired in smokers (total score 10.3 (3.2) versus 5.6 (3.9); $t = -3.3$, $p = 0.001$). When smoking status (current, ex-smoker, or never smoker) was added to the multiple regression for the whole subject group, the total quality of life score was found to be significantly associated with smoking status as well as baseline FEV₁. However, because of the interrelationship between FEV₁ and smoking status, it was necessary to include an interaction term in the regression. When this was added it was significantly associated with quality of life score, and the relationship between quality of life score and smoking status itself was no longer significant, indicating that the effect of

Table 2 Factors associated with quality of life scores: multiple regression analysis

	Log total score	Log activities score	Log impacts score	Log symptoms score
FEV ₁ (standardised residuals)	B = -0.15 SE = 0.04 p < 0.0001	B = -0.18 SE = 0.05 p < 0.001	B = -0.16 SE = 0.05 p < 0.002	B = -0.13 SE = 0.06 p < 0.05
Log dose-response slope	B = 0.04 SE = 0.04 p = NS	B = 0.06 SE = 0.06 p = NS	B = 0.06 SE = 0.05 p = NS	B = 0.11 SE = 0.06 p = 0.05
Age	B = 0.0003 SE = 0.003 p = NS	B = 0.0003 SE = 0.003 p = NS	B = 0.002 SE = 0.004 p = NS	B = -0.006 SE = 0.005 p = NS
Sex	B = -0.05 SE = 0.07 p = NS R ² = 0.08	B = -0.16 SE = 0.1 p = NS R ² = 0.05	B = 0.02 SE = 0.01 p = NS R ² = 0.05	B = 0.10 SE = 0.1 p = NS R ² = 0.07

Table 3 Correlation between quality of life scores and bronchial responsiveness, and between quality of life scores and baseline forced respiratory volume in one second (FEV₁) in older and younger subjects

	Log total score	Log activities score	Log impacts score	Log symptoms score
Log dose-response slope				
Age < 65	r = 0.31 p = 0.001	r = 0.27 p < 0.005	r = 0.33 p < 0.001	r = 0.30 p = 0.001
Age ≥ 65	r = 0.08 p = NS	r = 0.07 p = NS	r = 0.01 p = NS	r = 0.16 p = NS
FEV ₁ (standardised residuals)				
Age < 65	r = -0.42 p < 0.001	r = -0.35 p < 0.001	r = -0.41 p < 0.001	r = -0.31 p < 0.001
Age ≥ 65	r = -0.51 p < 0.001	r = -0.40 p < 0.001	r = -0.51 p < 0.001	r = -0.42 p < 0.001

smoking status on quality of life was the result of the interaction between smoking and FEV₁, rather than an independent effect.

The effect of age on the relationship between quality of life and lung function was assessed by repeating the analysis with the subjects divided into two age groups: <65 years (n=106) and ≥65 years (n=121). Calculation of linear correlation coefficients for the two groups gave similar results to those for the whole group, except that in the older age group there was no correlation between the log dose-response slope and quality of life scores (table 3). However, multiple regression analysis revealed differences between the age groups: in subjects aged <65 years the total quality of life score was significantly associated with the log dose-response slope ($B=0.17$, $SE=0.05$, $p<0.001$) but not baseline FEV₁ ($B=-0.08$, $SE=0.06$, $p=NS$), whereas in the older group the opposite was true (log dose-response slope: $B=-0.02$, $SE=0.05$, $p=NS$; baseline FEV₁: $B=-0.18$, $SE=0.05$, $p=0.0005$).

Discussion

Our results confirm that obstructive airways disease impairs quality of life. We have found no relationship between quality of life and age or sex, but have shown significant relationships with baseline FEV₁ and with non-specific bronchial responsiveness. Both chronic airways obstruction and bronchial hyperresponsiveness were relatively common in our population. This may reflect the large numbers of current and ex-smokers in this inner city area. However, smoking status itself was not found to be independently associated with quality of life.

Although the relationships between FEV₁ and quality of life scores were statistically significant, the value of R^2 for the multiple regression calculations was low, indicating that variation in FEV₁ explains only a small amount of the variation in quality of life. This weak relationship between quality of life and lung function indices in patients with airways obstruction has been previously reported,²⁻⁵ and has led to the suggestion that variability between patients in perception of breathlessness is a more important determinant of disability than the degree of airways obstruction itself.¹⁸ Psychological assessment of patients with obstructive airways disease has shown that illness attitudes and beliefs are stronger predictors of breathlessness and exercise tolerance than are measures of airways obstruction.^{19,20}

Although perhaps under-rated by doctors as a cause of distress, our results show that airways obstruction is associated with significant emotional dysfunction and limitation of activities. This impact of respiratory symptoms on activity was highlighted by a large population survey of elderly people in 1976²¹ in which 17% of housebound individuals or those confined to bed identified "pulmonary conditions" as the cause of their immobility and were second only to "arthritis, rheumatism" as the most common factor reducing independence.

The St George's Questionnaire is a disease-specific quality of life score designed for use in

subjects with airways obstruction. As such, it has not been validated in a general population sample. In the current study subjects with no airways disease tended to record very low quality of life impairment, particularly for the Symptoms score. This produced a skewed distribution of quality of life scores. St George's Questionnaire scores have been shown to be independent of age in subjects aged up to 75 years,⁸ but the questionnaire has not been validated in older subjects. The lack of correlation between quality of life scores and age in the current study suggests that the questionnaire is also valid in the elderly. However, the mean Activities score was higher for older subjects, indicating reduced activity levels with age.

Interestingly, where other studies have shown a change in quality of life with increasing age in subjects with asthma or obstructive airways disease, this has generally been an improvement in quality of life in older subjects.³⁻⁶ This has led to the suggestion that older subjects may be more tolerant of the effects of airways obstruction due to a reduction in their normal activity levels or in their expectations of life. It has been shown that older adults describe less severe symptoms than younger adults when exposed to the same degree of methacholine-induced bronchoconstriction.²² However, there is no evidence for a general decrease in the reporting of distressing symptoms by the elderly – indeed the opposite may be true.²³ The results of the current study do not confirm a reduction in the impact of obstructive airways disease on quality of life in older people.

Our results show that the interrelationships between bronchial responsiveness, baseline FEV₁, and quality of life scores change with age. The reasons for this are not clear. Mortagay *et al* have described a cluster of respiratory symptoms representing "bronchial irritability" which are associated with increased bronchial responsiveness in young adults.²⁴ However, the predictive value of these symptoms for increased bronchial responsiveness is much lower in the elderly.¹ Since respiratory symptoms affect quality of life, the lack of "bronchial irritability" symptoms in older adults with increased bronchial responsiveness may reduce the strength of the relationship between bronchial responsiveness and quality of life in this age group. Alternatively, our results may reflect a change in the interaction between baseline FEV₁ and bronchial responsiveness with age, rather than a change in their interaction with quality of life.

Schrier *et al* have also shown that obstructive airways disease is associated with impairment of quality of life in adults over a wide age range.² However, it is not clear whether quality of life was related to age in this study. The influence of increased bronchial responsiveness on quality of life was studied in young asthmatics by Malo *et al*²⁵ who found the mean quality of life score to be weakly but significantly correlated with baseline FEV₁ and non-specific bronchial responsiveness, as in the current study.

In summary, we have measured quality of life, airways calibre, and non-specific bronchial responsiveness in a population sample over a wide age range and have shown significant correlations between quality of life and both baseline FEV₁ and non-specific bronchial responsiveness. Multiple regression showed a significant independent relationship between quality of life and FEV₁ in older subjects, and between quality of life and non-specific bronchial responsiveness in younger subjects. However, the amount of variability in quality of life attributable to changes in FEV₁ and non-specific bronchial responsiveness is small. The impact of obstructive airways disease on quality of life does not decrease with advancing age.

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Detection of the multidrug resistance marker P-glycoprotein by immunohistochemistry in malignant lung tumours

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Abstract

Background - The multidrug resistance marker P-glycoprotein (P-gp) was studied immunohistochemically in 78 primary malignant lung tumours. P-gp is a 170 kD transmembrane ATP dependent drug efflux pump which has been shown to be important in the resistance of some tumours to chemotherapy. Certain normal tissues express P-gp and tumours derived from these tissues are often insensitive to cytotoxic agents, showing raised P-gp levels innately or following chemotherapy or radiotherapy.

Methods - Samples from 78 patients undergoing surgery for primary malignant lung tumours were snap frozen and stained immunohistochemically using the monoclonal antibody C219 which reacts with a P-gp epitope. None of the study group had received chemotherapy or radiotherapy before surgery was performed.

Results - Twenty seven of the 78 lung tumours (34.6%) showed immunohistochemically detectable levels of P-gp which varied with tumour type; 17 of 54 squamous cell carcinomas (31.5%), seven of 15 adenocarcinomas (46.7%), and neither of two small cell carcinomas showing positive staining. In six of seven cases normal respiratory epithelium present showed the presence of P-gp.

Conclusions - P-gp is immunohistochemically detectable in frozen tissue from a proportion of malignant lung tumours before exposure to radiotherapy or drugs associated with multidrug resistance. It may have a role in tumour resistance to cytotoxic drugs, but further clinical studies will be required to evaluate any correlation between P-gp levels and response to treatment.

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Keywords: multidrug resistance, P-glycoprotein, lung carcinoma.

as an ATP dependent drug efflux pump, reducing intracellular drug concentrations and thereby producing resistance to a large number of structurally unrelated cytotoxic agents.^{2,3} These include vinca alkaloids, anthracyclines, and epipodophyllotoxins. P-gp has also been observed in drug resistant strains of the malaria parasite *Plasmodium falciparum*.⁴

Certain normal human tissues have plasma membrane P-gp, with highest levels being observed typically in tissues with an excretory or secretory function such as colonic epithelium, adrenal, kidney, and liver tissue.⁵ Interestingly, tumours derived from these tissues are often insensitive to cytotoxic agents.

In vitro and in vivo studies have identified increased *mdr1* gene expression and its product P-gp in several human tumours and cell lines.^{5,6} Some workers have reported a correlation between innate and acquired multidrug resistance and P-gp expression, suggesting that its presence may be an indicator of resistance to chemotherapy. Inhibition of the pump action of P-gp by verapamil and other agents has been shown to increase cytosensitivity to chemotherapeutic drugs in certain cases.^{7,8}

Lung cancer is one of the commonest human malignancies and carries a poor prognosis. Non-small cell lung carcinomas generally show a poor response to chemotherapy, but the reasons for this are largely unknown. Mechanisms of multidrug resistance probably have a pivotal role in this process. There has recently been some renewal of interest in chemotherapy for non-small cell lung carcinoma⁹ with significant response rates in a number of trials,¹⁰ especially when used as an adjunct to surgery.^{11,12} Small cell lung carcinoma often shows a temporary response to chemotherapy, but treatment is largely palliative with little chance of a long term cure.

This study evaluates the expression of P-gp in 78 primary malignant lung tumours unexposed to the potential modulating effects of radiotherapy or chemotherapeutic agents using the monoclonal antibody C219 which recognises the *mdr1* gene product P-gp.

Methods

Tumour tissue was obtained from 77 patients undergoing lobectomy for primary malignant lung tumours, immediately snap frozen in liquid nitrogen, and stored at -80°C. In one patient material was obtained during mediastinoscopy and similarly treated. None of the

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Cytotoxic drug resistance is a major problem in cancer chemotherapy. The resistance of neoplastic cells to cytotoxic agents may be innate or acquired and occurs by a number of mechanisms, one of which is associated with the presence of a 170 kD transmembrane protein, P-glycoprotein (P-gp).¹ This is a product of the multidrug resistance gene *mdr1*, which acts

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